Development and Evaluation of a Home-Based Exercise Intervention for Frail Older People

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Declaration

I, Andrew Paul Clegg confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

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Abstract

Background

Frailty is common and is associated with important adverse health outcomes. There is evidence that exercise may influence the biological mechanisms of frailty and improve adverse outcomes. This thesis describes the development and evaluation of the Home-Based Older People's Exercise (HOPE) programme - a home-based exercise intervention for frail older people.

Methods

The MRC framework for the development and evaluation of complex interventions was used to develop and evaluate the HOPE programme. The development process synthesised information from four key domains: a systematic literature review; a process of intervention modelling work incorporating multiperspective focus group meetings; a review of behaviour change techniques and a review of international exercise guidelines. Following development, the HOPE programme was evaluated in a pilot randomised controlled trial. The primary outcome was mobility, measured using the Timed-Up-and-Go test (TUGT). Secondary outcomes included activities of daily living (ADL), quality of life and depression.

Results

The systematic review identified preliminary evidence that exercise may improve outcomes for frail older people. A grounded theory analysis of the multiperspective focus group meetings identified the important challenges faced by frail older people, along with motivators and barriers to exercise. The results were synthesised into the HOPE programme, which is a 12 week home-based exercise intervention. 60 participants were recruited to the HOPE trial. Mean age was 78 years. Baseline characteristics were similar in the two groups. There was a non-significant trend towards an improved outcome in the intervention group (mean adjusted between group difference in TUGT 16.7s, 95% CI -33.3, 66.6s). There were no differences in any of the secondary outcomes.

Discussion

The HOPE trial has provided valuable process, resource, management and scientific data to guide the development of a future definitive RCT and has provided important information to help inform future research involving frail older people.

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Supplementary Material

The three manuals that comprise the HOPE programme are provided as supplementary material in the CD attached to the rear cover of this thesis.

Index of Abbreviations

Aβ	amyloid beta
α-MSH	α-melanocyte stimulating hormone
ACSM	American College of Sports Medicine
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease
ADL	activities of daily living
AE	adverse event
AHA	American Heart Association
AMED	Allied and Complementary Medicine Database
ANCOVA	analysis of covariance
ARMD	age-related macular degeneration
ATM	ataxia telangiectasia mutation
ATP	adenosine triphosphate
BCT	behaviour change techniques
BDNF	brain derived neurotrophic factor
BER	base excision repair
BHPS	British Household Panel Survey
BMI	body-mass index
BMI1	polycomb group gene BMI1
CED-D	Centre for Epidemiological Studies depression scale
CFAS	Cognitive Functioning and Ageing Study

CFS	Clinical Frailty Scale
CGA	comprehensive geriatric assessment
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CM	case manager
CNS	central nervous system
CoQ	coenzyme Q
COX	cyclooxygenase
CR	caloric restriction
CRH	corticotrophin releasing hormone
CRP	C-reactive protein
CSHA	Canadian Study of Health and Aging
CT	control theory
CTRU	Clinical Trials Research Unit
CXCL-10	CXC chemokine ligand-10
DFLE	disability-free life expectancy
DH	Department of Health
DNA	deoxyribonucleic acid
EFS	Edmonton Frail Scale
ELSA	English Longitudinal Study of Ageing
EMBASE	Excerpta Medica Database
EQ-5D	EuroQol Group 5-Dimension Self-Report Questionnaire
EU	European Union
FADH2	reduced flavin acid dinucleotide

FI	Frailty Index
FRS	Family Resources Survey
GABA	γ-aminobutyric acid
GC	glucocorticoid
GDS	Geriatric Depression Scale
GH	growth hormone
GHS	General Household Survey
GP	general practitioner
GP	glutathione peroxidase
GR	glucocorticoid receptor
GRCS	Global Rating of Change Score
H2O2	hydrogen peroxide
HLE	healthy life expectancy
HOPE	Home-Based Older People's Exercise
HP	hypothalamic-pituitary
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
HR	homologous recombination
HSC	haemopoeitic stem cell
ICC	intra-class correlation coefficient
ICF	International Classification of functioning, disability and health
ICH-GCP	International Conference on Harmonisation - Good Clinical Practice

IFN-γ	interferon-γ
IGF	insulin-like growth factor
IL-1	interleukin-1
IL-1β	interleukin-1 beta
IL-6	interleukin-6
IL-10	interleukin-10
IMB	information-motivation-behavioral skills model
IR	ionising radiation
ISRCTN	International Standard Randomised Controlled Trial Number
LE	life expectancy
LPS	lipopolysachharide
MCI	mild cognitive impairment
MCID	minimum clinically important difference
MHADIE	Measuring Health and Disability in Europe
MMP3	matrix mettaloproteinase 3
MND	motor neuron disease
MPO	myeloperoxidase
MPP	1-methyl-4-phenylpyridinium ion
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRC	Medical Research Council
mRNA	messenger ribonucleic acid
NA	not available
NAD	nicotinic acid dinucleotide
NADH	reduced nicotinic acid dinucleotide

NADHDH	reduced nicotinic acid dinucleotide dehydrogenase
NER	nucleotide excision repair
NGF	nerve growth factor
NHEJ	non-homologous end-joining
NHS	National Health Service
NIHR	National Institute for Health Research
NO	nitric oxide
NOO	peroxynitrite
NOX	NADPH oxidase
O2-	superoxide
OC	operant conditioning
OEP	Otago Exercise Programme
OPSI	office of public sector information
OR	odds ratio
p16/ARF	p16 protein/alternate open reading frame
p53	p53 protein
PA	physical activity
PCT	Primary Care Trust
PD	Parkinson's disease
PedRO	Physiotherapy Evidence Database
PGC 1α	prostaglandin C1α
PGE2	prostaglandin E2
PLE	period life expectancy
pRb	retinoblastoma protein

PRISMA	preferred reporting items for systematic reviews and meta-analyses
Prs	peroxiredoxin
R&D	research & development
RCT	randomised controlled trial
REFS	Reported Edmonton Frail Scale
RNIB	Royal National Institute of Blind People
ROS	reactive oxygen species
SAE	serious adverse event
SC	satellite cell
SCogT	social cognitive theory
SD	standard deviation
SIRT	silent information regulators
SIRT1/SIRT6	sirtuin 1/6
SMD	standardised mean difference
SOD	superoxide dismutase
TGF-β	transforming growth factor-β
TLR	toll-like receptor
TNFα	tumour necrosis factor-α
TOR	target of rapamycin
TPB	theory of planned behaviour
TRA	theory of reasoned action
TUGT	timed-up-and-go test
UK	United Kingdom

UP	ubiquitin-proteosome
UP	uncoupling protein
US	United States
UV	ultraviolet radiation
VEGF	vascular endothelial growth factor
WBC	white blood cell
WHO	World Health Organisation

List of Publications

Clegg A, Barber S, Young J, Forster A, Iliffe S. Do home-based exercise interventions improve outcomes for frail older people? Findings from a systematic review. Reviews in clinical gerontology (in press)

Clegg A, Barber S, Young J, Forster A, Iliffe S. The Home-Based Older People's Exercise (HOPE) trial: study protocol for a randomised controlled trial. BMC trials 2011; 12: 143

Clegg A, Young J. The Frailty Syndrome. Clinical Medicine 2011; 11(1): 72-75

Dedication

for my wife, Laura, and my family

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1 Chapter 1. Introduction

1.1 Background

Frailty - Latin, *fragilita,* brittleness

Frailty is a common and important syndrome that is increasingly prevalent with advancing age. Whilst there is no internationally agreed definition of frailty a consensus view is emerging in which the physical phenotype of frailty is considered to develop as a consequence of complex biological interactions promoting cell senescence, leading to a cumulative decline in multiple physiological systems, particularly the brain, endocrine system, immune systems and skeletal muscle (1). This decline results in a loss of homeostatic reserve which can ultimately adversely affect the whole person, resulting in a vulnerability to a sudden health state change that can be triggered by relatively minor stressor events (2). The resulting frailty phenotype can be detected clinically, and measured by recording slow walking speed, muscle weakness, weight loss, low activity and fatigue (2, 3).

1.2 Epidemiology of frailty

A 2010 UK study investigated the prevalence of frailty amongst 638 community-dwelling people aged 64-74 years (4). The frailty prevalence

rate was 8.5% for women, and 4.1% for men. The Fried investigators (3) recorded a frailty prevalence rate of 6.9% in a cohort of 5201 men and women aged 65 years or more. Frailty rates of 3.2%; 9.5%; and 25.7% were recorded in age groups 65-70; 75-79; and 85-89 years respectively.

Frailty is self-perpetuating; its development results in a spiral of decline that leads to greater frailty and consequent risk of development of disability in older age. Recently, preliminary evidence has been reported that social factors, including social networks and socioeconomic status may also have a relationship with frailty (5). However, there remains significant uncertainty regarding the contribution of social vulnerability to the frailty syndrome and further work to characterise the key elements that comprise social vulnerability (6) and the relationship between social vulnerability and frailty is required (5).

Importantly, not all older people become frail as a result of the ageing process. A resistance to the development of frailty and a dissociation between chronological and biological age is often evident in older people (7). In a proportion of vulnerable older people, the interaction of a number of processes can promote the development of frailty.

A schematic overview of the complex interaction between molecular, cellular, physiological and clinical determinants of frailty is illustrated schematically in figure 1.1 and will be considered in greater detail.

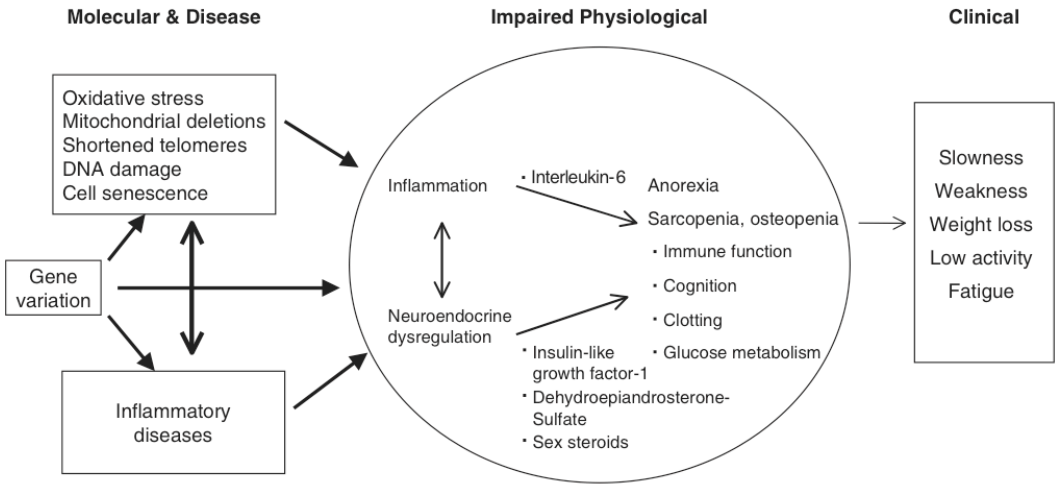


Figure 1.1. A schematic representation of frailty.

The figure highlights the complex relationship between genetic factors, molecular damage and inflammation causing cell senescence, leading to impaired physiology and loss of homeostatic reserve, which can be detected and measured using clinical markers of the frailty phenotype. Reproduced with permission from (1).

1.3 Frailty taxonomy

The utility of any system of medical taxonomy is reliant on its capacity to identify specific components that allow prediction of both natural history and response to therapeutic interventions (8). A robust system of medical taxonomy also requires consideration of the underlying biological principles of causality, without which precise unification of diagnosis and treatment is not possible (8). If significant progress into the management

of frailty is to be made, the fundamental causative biological events require identification.

A reliable system of frailty taxonomy should therefore predict both natural history and response to therapeutic intervention and be underpinned by biological principles of causality. Multiple systems of frailty taxonomy exist but each demonstrates variable utility in prediction of natural history, response to therapeutic intervention and consideration of underlying biological causality mechanisms. A 2011 systematic review identified 20 separate outcome instruments to measure frailty, with clear variation in clinical utility (9).

A shared central notion throughout the multiple frailty taxonomy systems is that frailty represents increased vulnerability to adverse health outcomes (10). There have been considerable recent efforts to form an international consensus on frailty that recognises vulnerability to adverse outcomes as a central feature. The two principal emerging models of frailty are the Fried phenotype model (3) and the Canadian Study of Health and Aging (CSHA) Frailty Index (11).

1.3.1 The Fried phenotype model

In order to investigate frailty, Fried et al (3) operationalised five core biological components to provide evidence for a frailty phenotype that is clinically recognisable and demonstrates predictive validity. When present

in combination the five core components have the potential to interact and cause a 'critical mass' that identifies the frailty syndrome. The core components (and their operationalised indicators) are presented in table 1.1.

Core component	Operationalised indicator
Weight Loss	Self-reported weight loss of more than 10 pounds or recorded weight loss of ≥ 5% per annum
Exhaustion	Self-reported exhaustion on CES-D depression score (3-4 days per week or most of the time)
Low Energy Expenditure	Energy expenditure <383 KCal/week (males) or <270 KCal/week (females)
Slowness	Standardised cut-off times to walk 15 feet, stratified for sex and height
Weakness	Grip strength, stratified by sex and BMI

Table 1.1. The five core components of frailty and their operationalised indicators.

CES-D, Centre for Epidemiological Studies depression scale; BMI, body mass index

Those individuals with none of the above indicators are characterised as robust older people. Those with one or two indicators are considered to represent an 'intermediate' or pre-frail group. Those with three or more

indicators are considered to represent a frail older population.

In a number of large prospective cohort studies, the Fried model of frailty has demonstrated utility in predicting the natural history and associated adverse health outcomes of frailty (3, 12, 13). The Fried model also identifies components of frailty, such as weight loss, slow walking speed and muscle weakness that are potential targets for therapeutic intervention. The model also considers the potential biological frailty causality mechanisms. The Fried model of frailty is supported in the frailty consensus statement from the American Geriatrics Society (1). However, the Fried model, which was developed retrospectively using data from the United States (US) Cardiovascular Health Study, does not consider the potential contribution of cognitive and socio-economic factors, which have an association with adverse health outcomes including disability (14, 15) and mortality (16).

1.3.2 The CSHA Frailty Index & Clinical Frailty Scale

The Frailty Index (FI) and Clinical Frailty Scale (CFS) were developed as part of the CSHA, a five-year prospective cohort study involving 10263 people aged 65 and older (11). The FI defines frailty as the cumulative effect of individual impairments - 'the more individuals have wrong with them, the more likely they are to be frail' (17). The FI is calculated by recording the presence or absence of 70 individual variables, which are a series of clinical deficits identified using signs, symptoms and abnormal

test results. These include limitations in activities of daily living, presence of cardiorespiratory problems, history of cognitive impairment and mood disorders. The FI demonstrates utility for prediction of natural history of disease and is highly reproducible but it is less practical for routine clinical use.

In order to develop a more practical FI that has greater utility for clinical use, the CSHA investigators constructed and validated a model based on specialist Comprehensive Geriatric Assessment (FI-CGA) (18). The FI-CGA is a valid and reliable method of frailty assessment that facilitates risk stratification and identification of future adverse health outcomes.

The CFS, validated against the FI, is a further model of frailty that is based on clinical judgment. Following a detailed clinical assessment the subject is categorised into one of seven domains, ranging from very fit to severely frail. The categories provide predictive information on the natural history of frailty, including five year risk of death and nursing home admission.

1.3.3 A comparison of frailty models

The phenotype model and FI have been compared in an analysis of data from 2305 participants in the CSHA (19). There was a moderate overall correlation between the two different measures (correlation coefficient, R = 0.65). There was a strong correlation with functional ability in both

models, but a weaker correlation with cognition in the phenotype model (R = -0.35) compared to the FI (R = -0.58). Furthermore, the continuous FI demonstrated greater discriminatory ability for those with moderate and severe frailty when compared to the categorical phenotype model.

The prediction of adverse health and social care outcomes by the FI and CFS is of great potential utility to both clinical decision makers and health policy planners. However, although the mathematical properties of the FI provide some insight into mechanisms of frailty, the prediction of response to therapeutic interventions is less clear. Furthermore, the FI provides limited insight into the fundamental biological causative mechanisms of frailty.

Although there are potential limitations regarding discriminatory function, the Fried phenotype model predicts natural history of frailty and potential response to therapeutic intervention. It also provides insight into the underlying biological causative mechanisms of frailty. As unification of diagnosis and treatment will be facilitated through greater understanding of biological causation, the insight into underlying biology provided by the Fried model is of particular value.

1.4 Understanding mechanisms of frailty

As with any clinical phenotype, identification of the frailty phenotype using the Fried criteria provides a framework around which understanding can

be structured, but precision can only come through a deeper understanding of the underlying frailty causality mechanisms (8). To understand causality, the fundamental principles of disease mechanism and pathophysiology must be considered. Disease mechanisms are based on the complex interplay between genes, epigenetics[1] and environmental exposures and it is through consideration of these factors that greater understanding of frailty will be gained (8).

Frailty and ageing are inexorably linked, but chronological and biological age are not synonymous. The genetic, epigenetic and environmental factors that underlie different vulnerabilities of people who are of the same chronological age will provide insight into the biological mechanisms of frailty.

Deeper understanding of frailty will be gained through consideration of ageing theory and genetic determinants of longevity, exploration of the biological mechanisms of molecular, cellular and tissue ageing and investigation of the relationship between organismal ageing and development of the frailty phenotype. These will be explored in greater detail below. The epigenetic factors that moderate genetic determinants and the influence of social vulnerability and the environment will also be

[1] Epigenetics are the mechanisms that regulate the differential expression of genes in different cells. Epigenetic mechanisms are discussed further in section 1.8.

explored. Finally, the relationship between frailty, disability and future population projections will be considered.

1.5 Ageing theory

1.5.1 The disposable soma theory of ageing

The disposable soma theory of ageing predicts that ageing results from the lifelong accumulation of unrepaired molecular and cellular damage. The theory predicts that the accumulation of damage is inherently stochastic (i.e. strongly influenced by chance) and is caused by multiple mechanisms that are regulated by a complex maintenance and repair network that exhibits plasticity in order to allocate finite energy resources to a number of competing processes. The theory predicts that the genes controlling this maintenance and repair network are the principal determinants of longevity (20, 21).

A schematic model of the interaction between multiple mechanisms of molecular and cellular damage leading to biological ageing is illustrated in figure 1.2. These mechanisms of molecular and cellular frailty will be considered in greater detail.

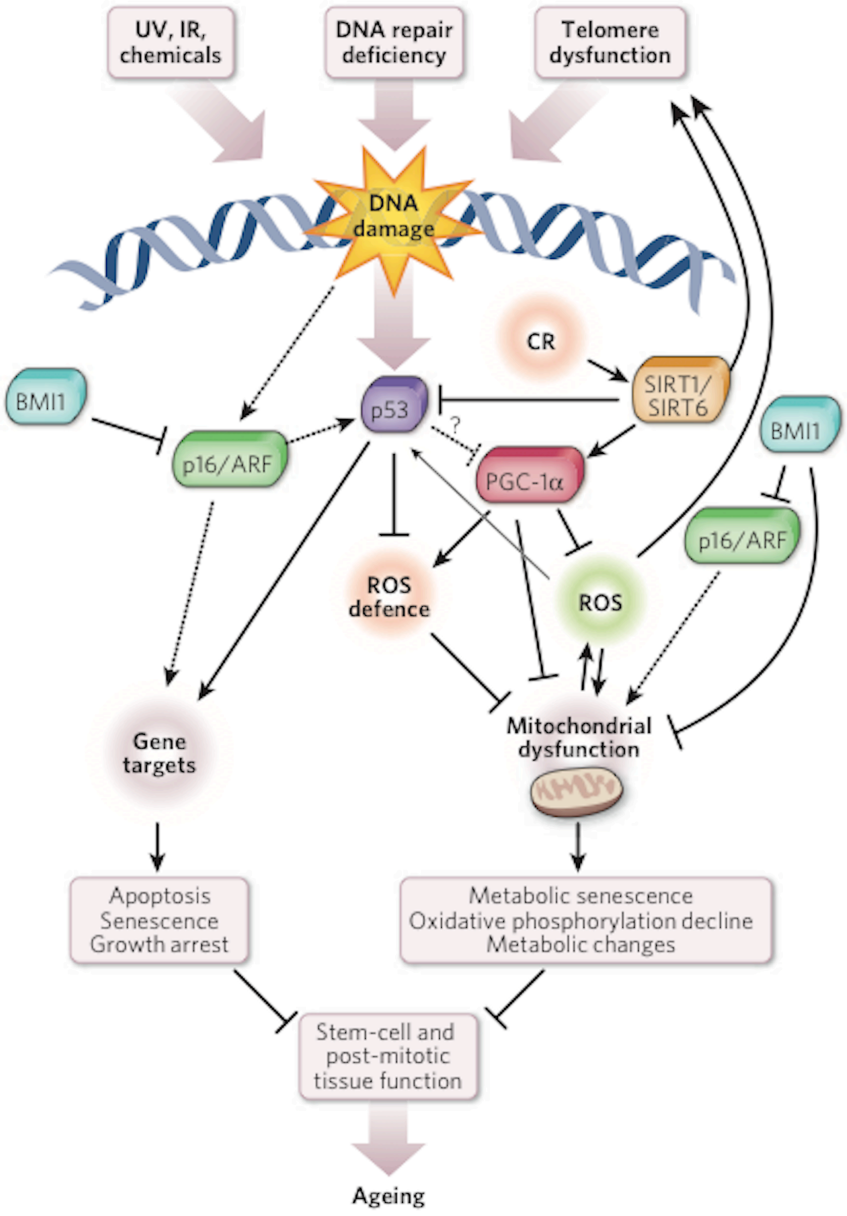


Figure 1.2. A model of interaction illustrating the accumulation of DNA damage through multiple interacting molecular and cellular mechanisms.

These interacting mechanisms cause metabolic and cellular senescence that ultimately leads to impaired tissue function and biological ageing. UV, ultraviolet radiation; IR, ionising radiation; BMI1, polycomb group gene BMI1; p16/ARF, p16 protein/alternate

open reading frame; p53, p53 protein; CR, caloric restriction; SIRT1/SIRT6, sirtuin 1/6; PGC 1α, prostaglandin C1α; ROS, reactive oxygen species. Reproduced with permission from (22).

1.6 Molecular frailty

1.6.1 DNA damage - a critical contributor to ageing

There is a growing consensus that loss of genetic information through accumulation of damage to the DNA molecule is a critical contributor to ageing (23, 24). DNA is present in both the cell nucleus and mitochondria and genetic mutations in both nuclear and mitochondrial DNA can give rise to a variety of inherited degenerative conditions that are characterised by accelerated ageing (24-26).

DNA damage can occur as a result of cell-intrinsic factors, including oxidative damage, defective DNA repair mechanisms and telomere dysfunction (23). DNA damage can also occur as a result of external factors, including ionising radiation and genotoxic drugs. The contribution of the important cell-intrinsic factors to the accumulation of DNA damage and how this leads to biological ageing will be explored in greater detail.

1.6.1.1 Free radical mediated oxidative DNA damage

Oxidative DNA damage is considered to be a central component in the biology of ageing, and is hypothesised to occur as a direct result of free

radical generation, as described in the Free Radical Theory of Ageing (27). The Free Radical Theory of Ageing was first postulated over 50 years ago and a large body of evidence has since accumulated to support the theory. The theory suggests that ageing results from the deleterious effects of intracellular free radicals (27). Free radicals are atoms, molecules and ions that contain an unpaired electron and are therefore chemically unstable. The instability of free radicals leads to high reactivity and potential to cause damage.

1.6.1.2 Reactive Oxygen Species (ROS)

Intracellular free radicals exist in the form of Reactive Oxygen Species (ROS) (27) which are generated in multiple cellular compartments and by multiple intracellular enzymes (28). Cellular ROS include superoxide, hydrogen peroxide and hydroxyl radicals (29). The large majority (around 90%) of ROS are generated in the mitochondria (28) and as the mitochondria contribute the principal ROS burden they are considered to be of key importance in oxidative DNA damage and biological ageing. Along with the mitochondria, the cell membrane, peroxisomes and cytoplasm also contain important enzymes that generate ROS (29).

1.6.1.3 Mitochondrial generation & metabolism of ROS

Mitochondria produce the majority of energy in animal cells through the release of energy generated during the passage of electrons along a series of respiratory enzymes in a process called oxidative

phosphorylation that results in the production of Adenosine Triphosphate (ATP) (30). This also results in the generation of mitochondrial ROS, and it is the process of oxidative phosphorylation that is therefore considered to provide the large majority of cellular ROS (28).

Following generation, rapid metabolism of mitochondrial ROS is facilitated by a number of intracellular scavenger enzymes, including Superoxide Dismutase (SOD), catalase, peroxiredoxin (Prx) and Glutathione Peroxidase (GP) (28). These scavenger enzymes exist in the mitochondria but can also be found in the cytoplasm and extracellular space. The mitochondrial production of ROS through oxidative phosphorylation and degradation via enzymatic scavenger reactions is illustrated schematically in figure 1.3.

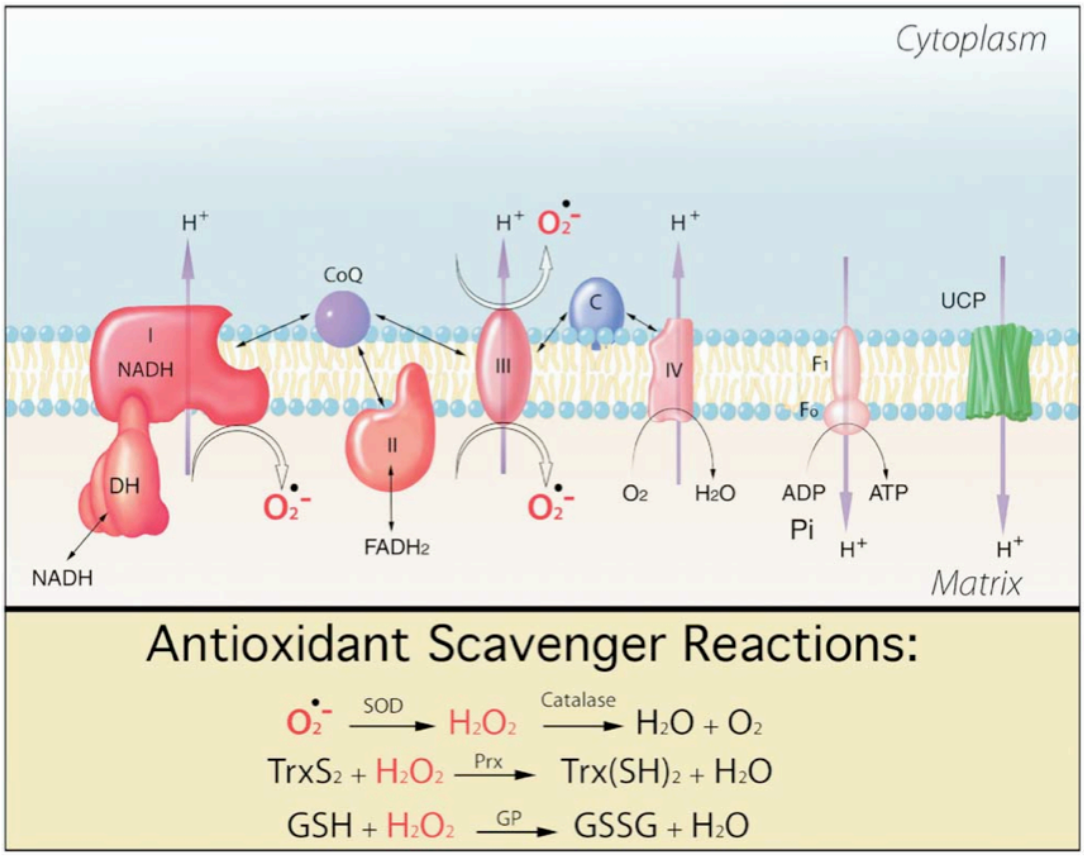


Figure 1.3. A schematic representation of mitochondrial production and degradation of Reactive Oxygen Species (ROS).

ROS, illustrated by $O_2^{\bullet -}$, are produced by oxidative phosphorylation complexes I - IV. ROS are then degraded by scavenger enzymes present in the mitochondria, cytoplasm and extracellular matrix. NADH, reduced nicotinic acid dinucleotide; NADHDH, reduced nicotinic acid dinucleotide dehydrogenase; CoQ, Coenzyme Q; FADH2, reduced flavin acid dinucleotide; UP, uncoupling protein; SOD, Superoxide Dismutase; Prx, Peroxiredoxin; GP, Glutathione Peroxidase. Reproduced with permission from (28).

1.6.1.4 Cell membrane and cytoplasmic generation of ROS

NADPH Oxidase (NOX) enzymes contained within the cell membrane and cyclooxygenase (COX) enzymes contained within the cytoplasm also contribute to the cellular ROS (28).

1.6.1.5 Phagocyte generation of ROS

When generated by NOX in phagocyte cells, ROS have an important immunological function. ROS are catalysed by SOD to form H_2O_2, which in turn serves as a substrate for peroxidases, for example neutrophil myeloperoxidase (MPO). Peroxidases drive the generation of antimicrobial hypohalous acids, which are converted to cytotoxic chloramines (31). This series of reactions is the basis for the powerful phagocyte respiratory burst, an essential component of the immune response.

1.6.1.6 Deleterious effects of ROS

A situation of oxidative stress exists when cellular ROS generation exceeds the metabolic capacity of scavenger enzymes such as SOD, Prx and GP (32). Cellular ROS, derived principally from mitochondria, but also from cell membrane, cytoplasmic, peroxisomal and phagocytic sources, have the potential to react rapidly with important biomolecules, including DNA, to cause oxidative damage that can accumulate in a stochastic manner.

Oxidative DNA damage in the form of single strand base damage, single strand nicks and double strand breaks can lead to irreplaceable information loss (24). This progressive, irreversible oxidative DNA damage is considered to be a powerful contributor to biological ageing.

Oxidative damage to proteins, lipids and carbohydrates can also occur as a result of cellular ROS (29). Although oxidative damage to proteins and lipids can accumulate gradually over time without immediate damage to the cell, evidence exists that the accumulation of damaged proteins can contribute to the development of a number of important disorders whose incidence increases with age, including cataract, Alzheimer's disease and Parkinson's disease (20).

1.6.1.7 Other effects of ROS

Although the effects of ROS have generally been considered to be deleterious, more recent evidence has begun to emerge regarding the potential role of ROS in other important cellular functions. ROS generating enzymes appear to be distributed throughout many cell types and a low-level formation of ROS may also play an important role in cell proliferation, cell apoptosis, receptor signalling and modification of the extracellular matrix (29)

1.6.2 Nuclear and mitochondrial DNA damage

Nuclear DNA (nDNA) is an important target for ROS induced damage and consequent ageing related changes. As there are only two to four copies of the nuclear genome per cell, compared to many thousands of copies of the mitochondrial genome, and as nDNA must last the lifetime of the organism it is considered particularly vulnerable to damage (24). However, mitochondrial DNA (mDNA) damage may also play an important role in ageing and age-dependent increases in damaged mDNA have been observed, particularly in post-mitotic tissues (e.g. brain) where the levels of mDNA damage are greater than nDNA damage (33). The proximity of mDNA to the main source of cellular ROS increases the vulnerability to oxidative damage, and the potential for a vicious cycle of damage has been proposed, whereby oxidative mitochondrial damage causes impaired mitochondrial function, increased ROS production and accelerated mDNA damage (28).

1.6.2.1 DNA damage and frailty

The association between oxidative DNA damage and frailty is beginning to be explored. Using the Fried criteria as the operational definition, a 2009 study of 90 elderly Chinese participants reported a significant association between oxidative stress and frailty, measured using the main oxidised DNA nucleoside, 8-hydroxy-2-deoxyguanosine (34). The study analysis incorporated a multivariate analysis that controlled for important

potential confounding variables including age, comorbidity, and smoking status.

In order to investigate the association between mitochondrial genetic variation and frailty susceptibility, a 2010 study compared the presence of mitochondrial DNA polymorphisms in 5275 frail and non-frail older people, diagnosed using the Fried criteria (35). Three mitochondrial DNA single nucleotide polymorphisms were significantly associated with frailty and independently associated with grip strength, supporting a role for mitochondrial variation in frailty and muscle strength in older age.

1.6.3 Defective DNA repair

Defective DNA repair is considered to be another important mechanism contributing to cellular and molecular damage associated with ageing. As DNA is critical to cellular function, a number of DNA repair mechanisms exist to maintain functional DNA in response to extrinsic and intrinsic damage. Beginning with initial detection of DNA damage by the ataxia-telangiectasia mutated (ATM) kinase, a collection of kinase enzymes and cellular proteins interact to facilitate DNA repair (23). DNA double-strand breaks are repaired by nonhomologous end-joining (NHEJ) and homologous recombination (HR) pathways, whereas single-strand lesions are repaired by base excision repair (BER) and nucleotide excision repair (NER) (23). Defective DNA repair capacity can predispose to premature ageing in a number of animal models (22) and most premature ageing

syndromes are caused by gene mutations in proteins involved in DNA repair (24). Conversely, increased levels of enzymes involved in the DNA repair pathway have been associated with increased life expectancy (36).

1.6.4 Telomere dysfunction

Telomeres are specialised structures situated at the ends of human chromosomes consisting of tandem nucleotide repeats (37). Telomeres help protect the ends of chromosomes from enzymatic damage to avoid loss of genetic information, help maintain chromosomal integrity and facilitate cell division (22, 38).

Repeated cell division results in replication-associated telomere shortening which can eventually compromise the protective function of telomeres. This shortening is detected by the DNA damage-repair machinery, which can buffer telomere shortening until a critical limit is reached, whereupon the cell can enter a state of proliferative arrest (cellular senescence), undergo apoptosis (programmed cell death) or give rise to neoplastic division (38). If cell proliferation progresses beyond this critical limit, often termed the Hayflick limit (39), further telomere erosion is precipitated, causing profound chromosomal instability (22). As part of the DNA molecule, telomeres are themselves subject to extrinsic and intrinsic damage and must undergo maintenance and repair. The enzyme telomerase maintains telomeres, but is only present in germ cells (testis and ovarian cells) and in certain adult stem cells.

Supported by the absence of telomerase in adult somatic cells, replication associated telomere shortening has previously been considered to function as a biological 'time-clock' that, following a pre-determined number of cell divisions, leads to natural cell senescence and protection against malignancy (40). However, there is evidence to suggest that telomere shortening may be a more complex process driven primarily by ROS mediated DNA damage (20). Increasing cellular ROS generation leads to increased telomere shortening and single strand DNA breaks accumulate at a rate dependent on applied oxidative stress (41). It is therefore plausible that telomere shortening, and its associated contribution to cell senescence, is driven principally by the level of cellular oxidative stress and can be accelerated (or reduced) under conditions of increased (or decreased) stress (20, 42).

Previous cohort studies have demonstrated positive correlations between telomere length, overall health profile and life expectancy (43, 44). Introduction of the catalytic subunit of telomerase into normal human cells has been demonstrated to stabilise telomere length and allow unlimited cell division without neoplastic transformation (45). Conversely, inherited mutations that affect the structure of telomerase can lead to accelerated ageing syndromes (46). Telomeres and telomerase are therefore considered to play a key role in the biology of ageing.

1.6.4.1 Telomeres and frailty

Although an association is biologically plausible, one study that investigated the association between telomere length and frailty in 2006 participants living in Hong Kong reported no association between frailty and telomere length (47).

1.6.5 Control of protein turnover

All cellular proteins are continually being degraded and replaced. Regulation of protein turnover is essential to control enzymes and proteins required for growth and metabolism, permit adaptation to new physiological conditions, facilitate immune system recognition of foreign peptides and selectively remove damaged proteins (48). Tight regulation is required, as destruction of an essential protein can deleteriously alter cell function. Similarly, failure to degrade and clear damaged proteins can lead to accumulation and alteration of cell function.

Precise regulation is important in certain physiological states, including fasting and inflammation, to increase protein breakdown in order to provide amino acids as both a muscle energy source and for hepatic gluconeogenesis (48).

1.6.5.1 Proteolytic systems

Proteins are degraded by a series of cellular proteolytic systems and different systems process different proteins. An overview of the proteolytic systems is provided in figure 1.4.

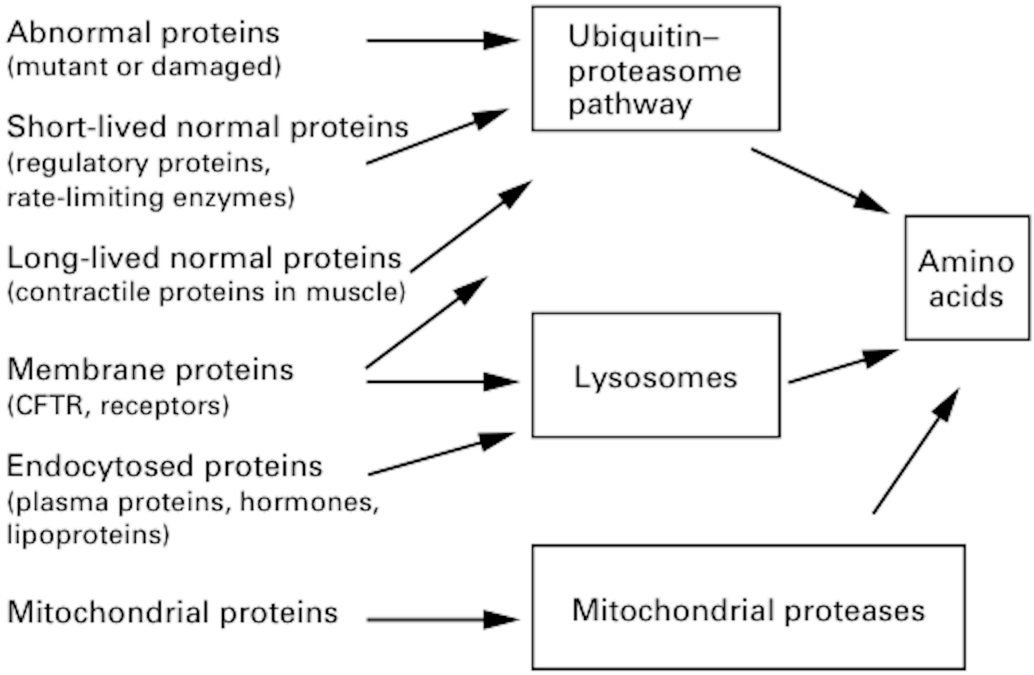


Figure 1.4. Roles of cellular proteolytic systems in the degradation of various classes of cell proteins.

Reproduced with permission from (48).

The ubiquitin-proteasome pathway is involved in the breakdown of most cellular proteins. Ubiquitin is a small protein cofactor that is enzymatically activated before covalent attachment to mark proteins for degradation. Once marked, proteins are identified by a large proteolytic complex, the proteasome, and undergo rapid degradation (49). Although it is potentially

capable of degrading multiple proteins, features of the ubiquitin-proteasome pathway allow remarkable selectivity and control of protein degradation (48).

Lysosomes are involved in the degradation of extracellular proteins, cell membrane proteins and bacteria. They are an important component of the immune response, but do not play an important role in the turnover of most cellular proteins, including muscle protein (48).

ROS can directly activate proteolytic pathways during periods of oxidative stress (50). However, ROS can also impair the efficiency of these proteolytic systems through oxidative structural changes and oxidation of regulatory enzymes (51). These changes to proteolytic systems may contribute to the development of cell senescence.

1.7 Cellular frailty

1.7.1 The cellular response to cumulative DNA damage

Multicellular organisms are composed of two fundamentally different cell types - mitotic cells that can divide (and can give rise to cancer), and postmitotic cells that are unable to divide (52). In mammals, mitotic cells include epithelial and stromal skin cells, vascular endothelial cells, intestine, liver, kidney and glial cells. Mitotic cells also comprise major components of the haematopoeitic system and include the

undifferentiated stem cells that provide differentiated tissue cells (53). Postmitotic cells include mature neurons, skeletal muscle cells, cardiac muscle cells and adipocytes (54).

A consequence of the finite energy resource allocation prediction of the disposable soma theory is that the multiple mechanisms of molecular damage that have been outlined can act in parallel to cause cumulative damage to the cell. This encourages the synthesis of a network theory of ageing which, rather than viewing these individual mechanisms in isolation, predicts the interaction of all of these mechanisms to cause biological ageing. An interactive network theory incorporates the possibility that multiple mechanisms of cellular and molecular damage may cause different outcomes in mitotic and postmitotic cells. Mitotic cells, which are actively proliferating, are more vulnerable to DNA mutations and telomere erosion. Non-proliferating post-mitotic cells are more vulnerable to the accumulation of abnormal proteins and waste products because, in contrast to mitotic cells, they are unable to synthesise new cellular components through cell division (20).

1.7.2 Cell senescence

Mitotic cells can undergo cell senescence, which is a fundamentally protective stress response characterised by irreversible inhibition of cell proliferation to prevent uncontrolled proliferation and malignant transformation. Cumulative DNA damage, oxidative damage and

oncogene activation are important triggers for cell senescence. To provide ongoing protection, maintenance of senescence can continue in the absence of the initial stress trigger (55). Importantly, although cell senescence is a fundamentally protective response, the cumulative effect of a growing number of senescent cells has the deleterious consequence of impaired tissue structure and organ function that can ultimately manifest in recognisable disease and organismal ageing (53).

Cellular senescence is restricted to mitotic cell types as these cells have the potential to divide, and hence undergo malignant transformation. Post-mitotic cells, which have lost the ability to divide, do not undergo senescence as it is currently defined but instead demonstrate important features that may represent a senescence equivalent (53). For example, post-mitotic neurons accumulate age-related oxidative DNA damage that can adversely influence synaptic function, protein transport and mitochondrial function, which can potentially contribute to impaired neuronal function.

1.7.3 Pathways to cell senescence

Cumulative DNA damage has the potential to compromise critical genetic information and appears to precipitate a protective cascade that begins with initial detection of damage by ATM kinase. Following detection, ATM kinase activates multiple subsequent downstream factors that can ultimately induce cell senescence (23, 55).

Although multiple different stimuli can induce cell senescence, activation appears to converge on one or both of two downstream pathways (52). One critical downstream pathway is governed by the p53 tumour suppressor protein. A second important downstream pathway mediating cellular senescence is the p16/pRb pathway.

1.7.3.1 The p53 pathway

The p53 protein is a key regulator of the cell cycle and is activated by DNA damage to induce cell cycle arrest, senescence, or apoptosis through alteration of target gene transcription (56, 57). Although experimental inactivation of p53 in senescent cells can completely reverse growth arrest (58), this arrest cannot be reversed by physiological signalling (52).

Animal models which have been induced to express activated p53 demonstrate early ageing phenotypes, with reduced physical activity, osteoporosis, organ atrophy and diminished stress tolerance, whilst at the same time exhibiting resistance to spontaneous tumour development (57). It is considered likely that p53 induces cellular senescence in an attempt to protect the organism against tumour development but this protective mechanism may ultimately accelerate organismal ageing.

1.7.3.2 The p16/pRB pathway

Oncogenes and other types of stress can induce the activation of the tumour suppressor p16, which in turn activates pRB, leading to irreversible cell senescence that cannot be overcome by inactivation of p53, pRB or both (59). The p16/pRB pathway causes cell senescence by reorganisation of cellular chromatin, the tightly bound DNA/protein complex that constitutes chromosomes (37).

1.7.3.3 Relationship between p53 and p16/pRB pathways

There is a growing consensus that the p53 pathway mediates cell senescence due to DNA damage and telomere dysfunction, whilst the p16/pRB pathway mediates senescence due to oncogene activation, chromatin disruption and cell stresses (59).

The roles of p53 and p16/pRB in the senescence response are illustrated in figure 1.5.

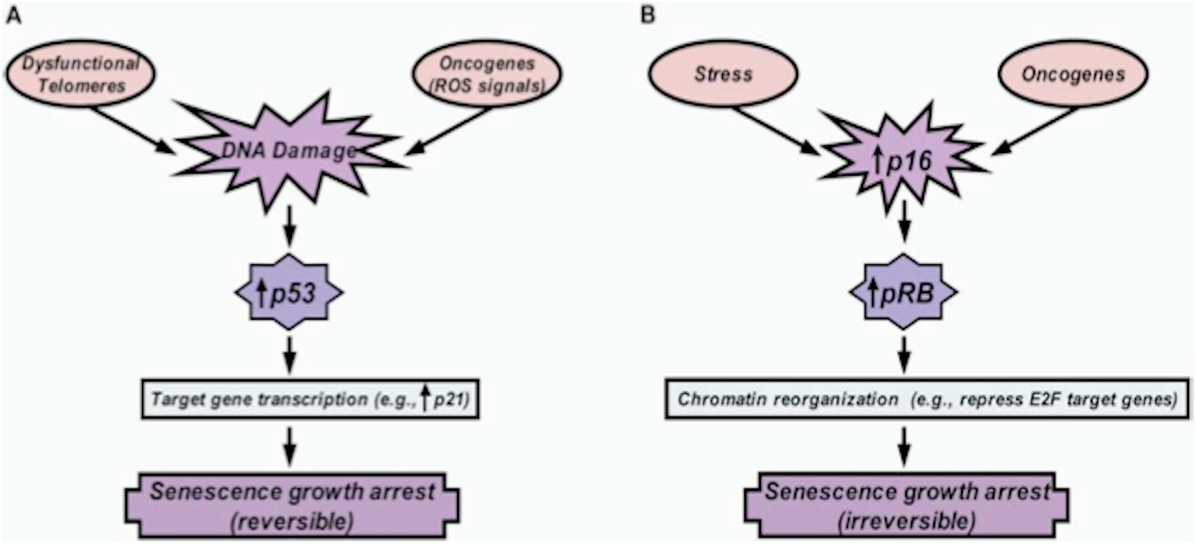


Figure 1.5. Roles of the p53 and p16/pRB pathways in the senescence response.

A) The p53 pathway to senescence. Detection of DNA damage activates the p53 damage response. The transcription of p53-dependent genes induces a senescent-like growth arrest that cannot be reversed by physiological mechanisms but is reversible upon inactivation of p53. B) The p16/pRB pathway to senescence. Oncogenes and other types of stress induce p16, which activates pRB causing cell senescence through reorganisation of chromatin that cannot be reversed by inactivation of p53, pRB or both. Reproduced with permission from (59).

Although cell senescence is associated with organismal ageing there is an absence of evidence regarding the relationship between cumulative cell senescence and phenotypic frailty.

1.8 Epigenetic factors

Human cells contain identical genetic information. Certain genes that regulate essential cellular functions are expressed in all cells. However, some genes are required in particular cells to provide different proteins that enable specialised physiological function (60). Epigenetic mechanisms regulate the differential expression of genes in certain cells but do not result in a change to gene sequence or structure (61). DNA methylation and histone modification are considered to be the key mechanisms involved in the epigenetic regulation of gene expression (61). These mechanisms, which are responsive to physiological and environmental cues and demonstrate reversibility, may have particular importance in the determination of physical phenotype and ageing (61, 62). As epigenetic mechanisms are responsive to environmental cues, they provide an attractive potential link between environmental factors, ageing and disease (63).

Epigenetic mechanisms have been investigated in the post-mitotic cells of the brain and have been associated with the development of synaptic plasticity and memory (64). A growing body of literature supports the presence of an association between epigenetics, brain ageing and cognitive impairment (65). Although there is evidence to support a potential link between epigenetics and ageing, the role of epigenetics in frailty is currently unclear and represents an area for future research. Importantly, as DNA methylation and histone modification are potentially

reversible, epigenetic mechanisms may represent a potential target for future pharmacological therapeutic intervention.

1.9 Summary of molecular and cellular frailty

Multiple, interacting molecular mechanisms have the potential to cause cumulative DNA damage that is regulated by a complex maintenance and repair network. Cumulative damage is detected by a series of intracellular proteins that can initiate one or both of two pathways that ultimately induce cell senescence when a critical level of DNA damage is accumulated or oncogenes are expressed.

Senescent cells remain metabolically active and influence the surrounding microenvironment leading to extracellular remodelling, inflammation and a potential increase in risk of malignant transformation of surrounding cells. The stochastic aspect of cell senescence means that senescent cells accumulate alongside relatively undamaged cells. This cell senescence is irreversible under normal physiological circumstances and protects the cell from undergoing malignant change but has the potential consequence of compromised tissue function, which is detected as phenotypic ageing. The cumulative volume of senescent cells that is required to cause impaired organ physiology is currently unknown and is an important area of ongoing research.

1.10 Frail tissues

1.10.1 Alteration of tissue structure and function by senescent cells

As the total number of tissue cells is relatively constant, the accumulation of senescent cells may alter tissue architectural structure and compromise essential renewal and repair mechanisms (59). This alteration of tissue structure may impact directly on physiological function.

Although senescent cells are unable to progress through the cell cycle, they remain metabolically active (53). Induction of cell senescence by p53 and p16/pRB pathways leads to the upregulation of a number of genes encoding enzymes, growth factors and cytokines that can alter tissue structure and function through alteration of the surrounding microenvironment (59). For example, senescent fibroblasts increase the secretion of proteins that remodel the extracellular matrix and mediate local inflammation (53, 66).

The upregulation of local regulatory proteins is considered to be the more likely mechanism underlying alteration of tissue structure and function by senescent cells (59). This alteration of the tissue microenvironment by senescent cells may also promote the development of malignancy by stimulating growth and angiogenesis in nearby pre-malignant cells (53, 59).

A further potentially important consequence of senescence may be the impact on stem cells, which are found in adult tissues and promote repair and renewal. Both direct stem cell senescence and indirect effects on stem cells from surrounding senescent cells may affect the proliferation and differentiation of tissue stem cells, ultimately compromising tissue regeneration (59).

A schematic overview of the potential alteration of tissue structure and function by senescent cells is provided in figure 1.6.

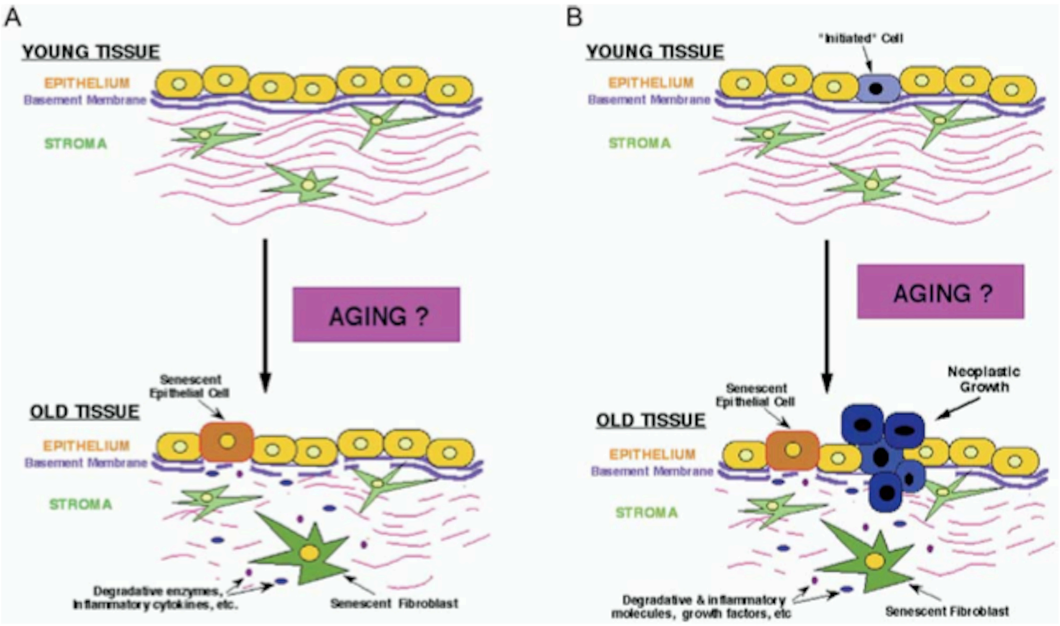


Figure 1.6. The contribution of senescent cells to ageing and age-related pathology, including cancer.

A) Senescent cells may disrupt normal tissue structure and function by producing degradative enzymes and inflammatory cytokines that can disrupt tissue structure and function.
B) Senescent cells may promote cancer progression. Both senescent cells and cells with preneoplastic mutations accumulate with age, as does the probability of both occurring in close proximity. When this occurs, molecules secreted by senescent cells may create a permissive microenvironment that allows the proliferation of preneoplastic cells. Reproduced with permission from (59).

Cumulative cell senescence can ultimately cause impaired organ physiology. The relationship between cell senescence and physiological impairment, and the relationship between physiological impairment and frailty will be considered.

1.10.2 Cell senescence and physiological impairment

The stochastic element of DNA damage and associated cell senescence implies that damaged senescent cells must exist alongside relatively undamaged actively dividing cells (20). Although senescent cells can disrupt the normal structure and function of tissues, the cumulative volume of senescent cells that is required to cause impaired organ physiology is currently unknown. There is only limited experimental data regarding loss of skin physiological function due to cell senescence in

accelerated ageing syndromes, and the cumulative contribution of cell senescence to impaired organ physiology is an area of ongoing research (67).

1.11 Frail organ systems

The brain, endocrine system, immune system and skeletal muscle are considered to be the organ systems that play a central role in the development of frailty. The relationship between cell senescence and physiological impairment in these interacting organ systems and the effects of cumulative physiological impairment to promote frailty will be explored.

1.12 The frail brain

Human ageing is accompanied by structural and neurophysiological changes in the brain. These changes are associated with varying degrees of cognitive decline and dementia in a significant proportion of the population (68).

Although age is the dominant risk factor for the development of Alzheimer's disease (AD), cognitive decline is frequently observed in advanced age even in the absence of detectable pathology such as AD and a fundamental question is whether the cognitive decline of ageing is clearly distinct from the pathological processes associated with such

diseases (69, 70). Loss of hippocampal neurons is observed in both normal ageing and AD, but neuronal loss predominates in certain areas of the hippocampus in AD when compared to normal ageing, suggesting a pathological distinction between the two (71). However, other parameters including synapse loss, amyloid plaques and neurofibrillary tangles can be extensive in AD, but are also present in variable densities in normal brain ageing (68).

The mechanisms that underlie brain ageing and the associated pathophysiological consequences will be explored in greater detail.

1.12.1 Neuronal cell cycle

Central nervous system (CNS) neurons are classically described as postmitotic cells, i.e. that they are in a state of permanent cell cycle arrest. However, maintenance of cell cycle arrest is an active process and highly differentiated neurons must constantly keep their cell cycle in check, otherwise re-entry into the cell cycle can be initiated, resulting in vulnerability to neuronal cell death (72). It has been postulated that neuronal cell cycle re-entry may be the cause of a number of neurodegenerative disorders, including Alzheimer's disease (AD), Parkinson's disease (PD) and motor neuron disease (MND) (72).

Interestingly, although there is global loss of higher cortical function with ageing, the loss of individual neurons in the majority of cortical regions in

the ageing brain is minimal (68). Given that neuronal loss is minimal, altered synaptic function, protein transport and mitochondrial function are potentially important mechanisms underlying the global loss of higher order neuronal function that is observed with ageing (68). In line with ageing theory, cumulative DNA damage and mitochondrial damage are considered to be important mediators of neuronal and brain ageing, in association with impaired cellular autophagy and abnormal microglial cell function (69, 73, 74).

1.12.1.1 ROS mediated neuronal DNA damage

Inherited deficiencies in components of the DNA damage-repair cascade are frequently associated with accelerated neuropathology, implying that DNA damage is important in neuronal ageing (69). Although ROS mediated DNA damage is inherently stochastic, certain DNA regions that are involved in synaptic function, protein transport and mitochondrial function appear to be particularly vulnerable to oxidative damage (75).

The neuron responds to detection of oxidative damage by upregulating DNA damage and repair genes, but if areas of neuronal DNA remain unrepaired they are silenced, leading to a state of transcriptional repression (68, 75, 76). As non-dividing post-mitotic cells do not undergo neoplastic transformation it may be advantageous for neurons to remain in this state, avoiding apoptosis even if DNA damage has accumulated

(69). This maintenance of neurons in a repressed state may also explain the observation that neuronal volume loss with ageing is minimal.

In the ageing human pre-frontal cortex, there is disproportionate down-regulation of genes encoding the inhibitory neurotransmitter γ-aminobutyric acid (GABA) (76). Although this alteration in the balance between excitatory and inhibitory neurotransmission could initially be compensatory, increased excitatory neurotransmission could eventually lead to excitotoxic neurodegeneration.

1.12.1.2 Reduced neuronal mitochondrial function

Brain (and muscle) cells are particularly dependent on mitochondrial function, being adversely affected in a number of inherited mitochondrial disorders (68). A progressive age-related reduction in neuronal mitochondrial gene expression causing impaired mitochondrial function through reduced expression of important oxidative phosphorylation proteins has been recorded in humans (75). Neurons with high metabolic demands, for example the large hippocampal pyramidal neurons, may be disproportionally affected by declining mitochondrial function and be rendered vulnerable to damage (68). The hippocampus is an area of the brain that coordinates the storage and retrieval of information and has been identified as an important mediator in the pathophysiology of cognitive decline and Alzheimer's dementia (77). In addition, the hippocampus is a key component of the stress response, sensing

increased glucocorticoid levels and relaying information to the hypothalamus in a negative feedback loop (78). Therefore, damage to hippocampal neurons has the potential to affect both cognition and the organismal response to stress.

However, the relationship between neuronal mitochondrial function and ageing is complex. Modestly reduced mitochondrial function can, in certain cases, increase overall longevity but a more severe reduction in mitochondrial function can shorten lifespan (79). It has been proposed that the initial decline in neuronal mitochondrial gene expression may be a protective mechanism to increase stress resistance, but further oxidative stress may reduce neuronal mitochondrial function to a level at which there is critical DNA damage that results in gene silencing and transcriptional regression (68).

1.12.1.3 Impaired cellular autophagy

Autophagy is a process of continuous cellular 'housekeeping' to dispose of unwanted or damaged cellular proteins (74). Under inhibitory regulation by the energy-sensing Target of Rapamycin (TOR) kinase system, damaged monomeric cellular proteins can be tagged by proteins such as ubiquitin and are then disposed of by a series of enzymatic degradation systems including the proteasome system (74). However, this system of degradation cannot handle more complex cellular protein microaggregates, which require intact autophagy systems. The

accumulation of protein microaggregates as inclusion bodies can be toxic to the cell and hence the autophagy system is an important protective mechanism, particularly in neurons, which are unable to grow and divide to eliminate waste products (74).

Autophagy involves the initial sequestration of protein aggregates in a double membrane vesicle and the subsequent delivery of the vesicle to an organelle termed the lysosome, which breaks down the sequestered protein. This occurs at a continuous low-level rate in a process termed basal autophagy. There is evidence that reduced basal autophagy in mice can lead to the formation of inclusion bodies similar to those seen in neurodegenerative diseases such as AD, and there is evidence that suppression of the regulatory TOR kinase system can extend lifespan (80, 81).

Whilst it has traditionally been considered that the inclusion bodies and protein aggregates such as amyloid are intrinsically toxic to neurons, it has more recently been proposed that they represent a relatively terminal phase of neurodegeneration as opposed to an important intermediate phase during which targeted interventions to prevent further decline may be successful (74). An overview of autophagy is provided in figure 1.7.

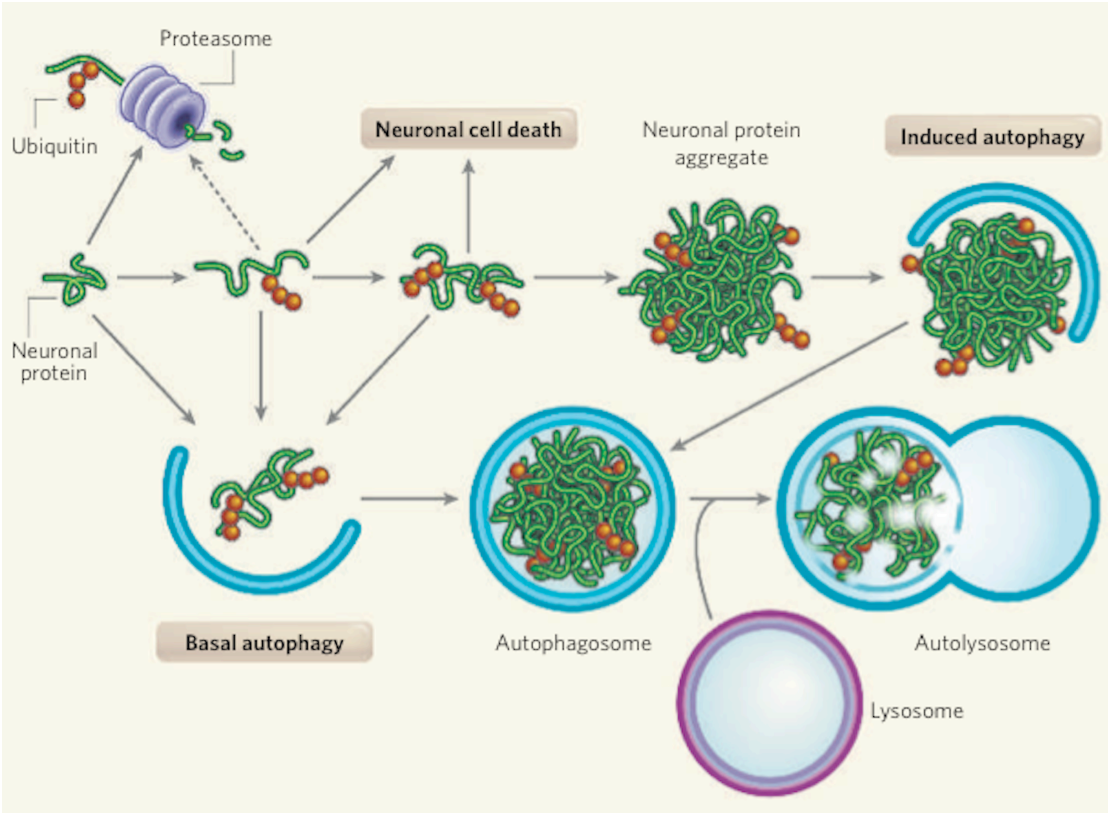


Figure 1.7. The role of autophagy in protecting against neuronal cell death.

Misfolded proteins are tagged with ubiquitin and degraded by the proteasome system. However, proteasome is unable to degrade certain proteins, which accumulate in the cytoplasm creating microaggregates and potentially causing cell death. Basal autophagy acts to keep levels of these microaggregates down to prevent toxic effects by sequestration for delivery to lysosomes. The folded proteins can also form large aggregates or inclusion bodies that can induce autophagy. These large aggregates may be more protective than harmful. Reproduced with permission from (74).

1.12.1.4 Abnormal microglial cell function

Microglia are the resident immune cell population of the CNS and are the CNS equivalent of macrophages. Microglia, in contrast to neurons, are cells that have the potential to divide (82, 83). In the healthy adult brain, microglia are found in a 'resting' state as a small cell body with fine projections and low expression of antigens (82). This resting microglial state is controlled by neuron-microglia contact, neuronal electrical activity and neurotransmitter actions (73). In response to brain injury and local inflammation, microglia migrate to the site of inflammation and proliferate to phagocytose dying cells and/or release cytokines to maintain the microenvironment and support injured neurons (73). In addition to local inflammation, microglia can be activated by systemic inflammation, with the result of an overall increase in brain inflammation (84).

In younger people the microglia response is protective. However, dystrophic microglial structural changes are observed in the ageing brain, including abnormal cytoplasm characterised by distorted projections, along with altered immune expression and inflammatory profile. These dystrophic changes are accompanied by alterations in microglial function, and microglia become primed to be over-responsive to small stimuli, which can potentially cause damage and neuronal death (73, 84, 85). These dystrophic changes and abnormal response to stimuli are believed to represent the microglial equivalent to cell senescence, and primed microglia are postulated to play an important role in the pathophysiology

of delirium, which is associated with important adverse consequences including increased morbidity and mortality (84, 86).

Increased numbers of dystrophic microglia have been observed in older people, and impaired microglial function has been reported in neuropathological conditions including AD (87). Microglial senescence, with its accompanying structural and functional changes, may compromise the immune function of the brain and contribute to the development of neurodegenerative disease through diminished neuroprotection (85). The exact mechanisms underlying microglial senescence are yet to be elucidated but are likely to include common mechanisms of DNA damage, telomere shortening and mitochondrial dysfunction. Indeed, significant microglial telomere shortening and reduced telomerase activity have been recorded in animal models of normal ageing, and these changes are accelerated by the presence of amyloid, suggesting that microglial cells may have an important role to play in the pathophysiology of age-related cognitive decline and AD (88).

A schematic representation of microglial overactivity leading to progressive neurotoxicity is provided in figure 1.8.

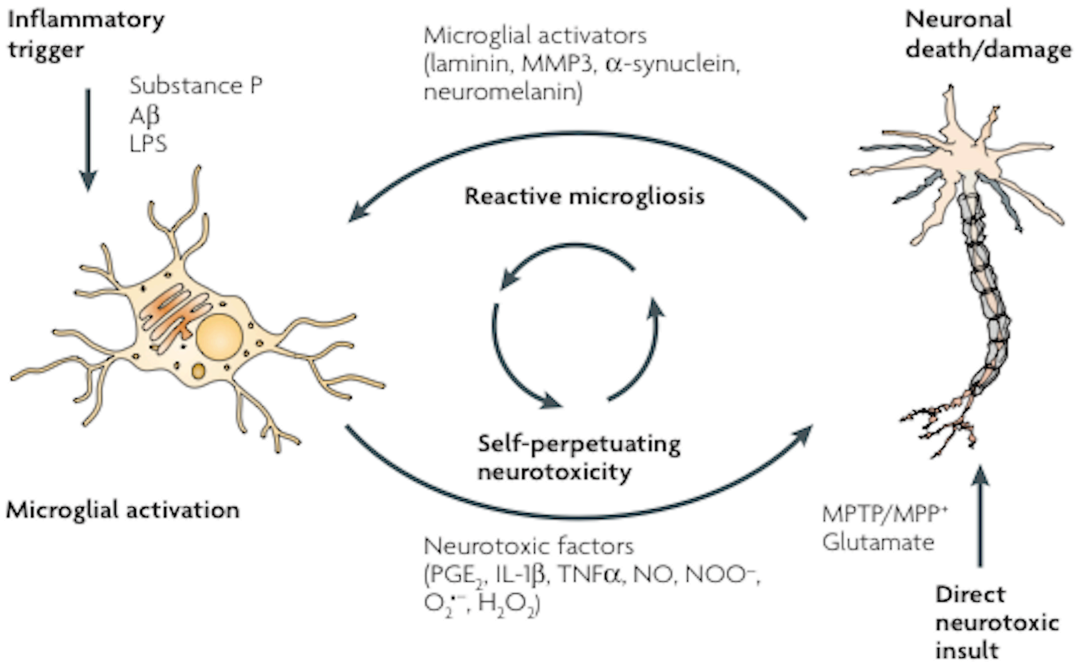


Figure 1.8. Reactive microgliosis drives progressive neurotoxicity. Microglia can become overactivated and cause neurotoxicity through two mechanisms. First, microglia can initiate neuron damage by recognising pro-inflammatory stimuli, such as lipopolysaccharide (LPS), becoming activated and producing neurotoxic pro-inflammatory factors. Second, microglia can become overactivated in response to neuronal damage, which is then toxic to neighbouring neurons, resulting in a perpetuating cycle of neuronal death. Aβ, amyloid beta; H2O2, hydrogen peroxide; IL-1β, interleukin-1 beta; MMP3, matrix mettaloproteinase 3; MPP, 1-methyl-4-phenylpyridinium ion; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NO, nitric oxide; NOO, peroxynitrite; O2-, superoxide; PGE2, prostglandin E2; TNFα, tumour necrosis factor-α. Reproduced with permission from (89).

1.12.2 Frailty, delirium and dementia

There is indirect evidence to support a biologically plausible association between frailty and delirium. Proxy markers of frailty, including age, cognitive reserve, cognitive impairment, comorbidity, disability and long-term care residence have all been identified as independent risk factors for delirium (90-92). The hippocampus is activated early in delirium and metabolically vulnerable hippocampal neurons may characterise the frail brain at risk of delirium (93).

There is accumulating evidence from observational studies to support a temporal association between frailty, cognitive impairment and dementia. A 2010 prospective cohort study including 750 older people without cognitive impairment at baseline reported that physical frailty was associated with increased risk of developing mild cognitive impairment (MCI) over 12 years of follow-up, controlling for depression, disability, vascular risk factors and vascular disease (94). MCI is a condition that is increasingly recognised as a precursor to dementia, and each one-unit increase in frailty (measured using grip strength, timed walk, body composition and fatigue) was associated with a 63% increase in MCI risk (hazard ratio, HR, 1.63, 95% confidence interval, CI, 1.27 - 2.08). A higher level of physical frailty was also associated with a faster rate of cognitive decline..

A 2007 cohort including 823 participants reported that frailty was associated with increased risk of AD during three years of follow-up (95). Using an operationalised frailty index, both baseline frailty and annual rate of change were associated with increased risk of AD. Each 1/10 of a unit increase in baseline frailty was associated with an approximately twofold increase in AD risk (HR 1.94, 95% CI 1.31 - 2.87) and each 1/10 of a unit increase in rate of change of frailty was associated with an approximately threefold increase in AD risk (HR 3.30, 95% CI 1.52 - 7.13).

1.13 The frail endocrine system

There is accumulating evidence that the endocrine system has a crucial role in the regulation of organismal ageing and frailty. The brain and endocrine system are intrinsically linked through the hypothalamo-pituitary (HP) axis, which controls the metabolism and energy use of the organism via the signalling action of a series of homeostatic hormones (68). Regulation of glucocorticoid (GC) secretion and insulin-like growth factor (IGF) signalling are considered to be of key importance, as deficits in these hormonal systems have been associated with adverse ageing profiles and frailty.

1.13.1 Glucocorticoid secretion and frailty

The hypothalamus receives and integrates multiple afferent inputs from diverse regions of the brain to coordinate the organismal response to stress and inflammation, partly through the control of GC secretion (96). Basal GC secretion is necessary for the normal function of many cells and levels are increased in response to virtually any stress, including physical and psychological stress, or the presence of inflammation, to provide the altered physiological requirements that promote survival (97). Peripheral cytokines such as IL-1 and IL-6 that are released in response to stress and inflammation have both direct and indirect effects on the hypothalamus to promote GC secretion (97). Circulating GC are subsequently sensed by the hippocampus, which suppresses hypothalamic stimulation of GC production in a negative feedback loop.

Uncontrolled inflammation has the potential to cause cellular damage, and a functional GC system is an important component of the homeostatic regulation of local and systemic inflammation. The loss of hippocampal neurons that is observed in both normal ageing and AD may impair the homeostatic control of the GC system, with the consequence of uncontrolled inflammation and increased cellular damage, promoting organismal ageing. Loss of homeostatic control of the GC system may itself promote further neurodegeneration, as chronically elevated levels of GC have been hypothesised to increase hippocampal neuronal damage (98). The loss of hippocampal neurons that is observed in both normal

ageing and AD may therefore promote a spiral of accelerated neuronal damage through impairment of the GC negative feedback loop, uncontrolled inflammation and neurotoxic effects of chronically elevated GC levels (68).

A recent cross sectional study involving 214 female participants reported that frailty, measured using the Fried criteria, was independently associated with chronically elevated diurnal cortisol levels, even after adjustment for depressive symptoms, which are themselves associated with increased cortisol (99). A link between chronically elevated cortisol and frailty is biologically plausible, as persistently high levels of cortisol have been associated with increased catabolism, leading to loss of muscle mass, anorexia, weight loss and reduced energy expenditure - the cardinal clinical features of frailty (50).

1.13.2 Insulin-like growth factor signalling and frailty

Insulin-like growth factors (IGFs) are a family of small peptides that increase anabolic activity in many cells. Promotion of neuronal plasticity and increased skeletal muscle strength are considered to be particularly important effects (100). The principal IGFs are IGF-1, IGF-2 and insulin. IGF-1 is synthesised in the liver in response to circulating Growth Hormone (GH) in a process that is regulated by the HP axis. A range of growth factors and hormones also stimulate local synthesis of IGF-1 by neurons, muscle cells and white blood cells (WBCs).

The local autocrine and paracrine actions of IGF-1 are considered to be important for the promotion of neuronal plasticity and increased skeletal muscle strength (100, 101). Age-related impairments in autocrine, paracrine and endocrine activity of IGF-1 are considered to be important in the development of neuronal senescence and sarcopenia (100, 101).

IGF-1 regulates the production of a number of transcription factors that influence the expression of multiple genes that are implicated in oxidative stress, inflammatory regulation and cellular autophagy (102). One important downstream transcription factor is DAF-16 and recent evidence suggests that this may play a key role in influencing organismal lifespan (103). Indeed, genetic variations in the IGF signalling pathway have been associated with increased life expectancy in humans (104).

Evidence is beginning to accumulate to support the hypothesis that IGFs play an important role in frailty. A 2004 cross-sectional study including 51 older participants reported significantly lower levels of IGF-1 in those who were identified as frail by the Fried criteria when compared to age-matched controls (105). An inverse correlation between IGF-1 and IL-6 levels was observed, identifying a potential relationship between IGF-1 and the frail immune system.

A 2009 cross-sectional study involving 696 older women from the US Women's Health and Aging Study identified a significant correlation between white blood cell counts and IGF-1. A complex U-shaped association between IGF-1, WBC count and frailty was also reported. Compared to a reference of high IGF-1 and low WBC counts, when IGF-1 levels were low, both low and high WBC counts were associated with increased risk of frailty. Conversely, when WBC counts were high, both low and high levels of IGF-1 were associated with frailty (106).

1.13.2.1 IGFs and the brain

IGFs promote neuronal survival by inhibiting apoptosis and can increase learning and memory in humans (68, 107). Primary neuronal changes in the hippocampus and hypothalamus may affect the IGF pathway, resulting in a predisposition for accelerated neuronal death and a consequent deterioration in physiological function (68).

1.13.2.2 IGFs and muscle

IGFs stimulate myogenic differentiation and induce skeletal muscle hypertrophy, with IGF-1 exhibiting greatest potency (100, 108). Amino acid uptake, protein production, glucose uptake and muscle cell proliferation are all stimulated by IGFs, which act principally via the IGF-1 receptor located on myocytes and skeletal muscle stem cells (100).

A schematic representation of the brain and endocrine system as a potential regulator of organismal ageing and frailty is provided in figure 1.9.

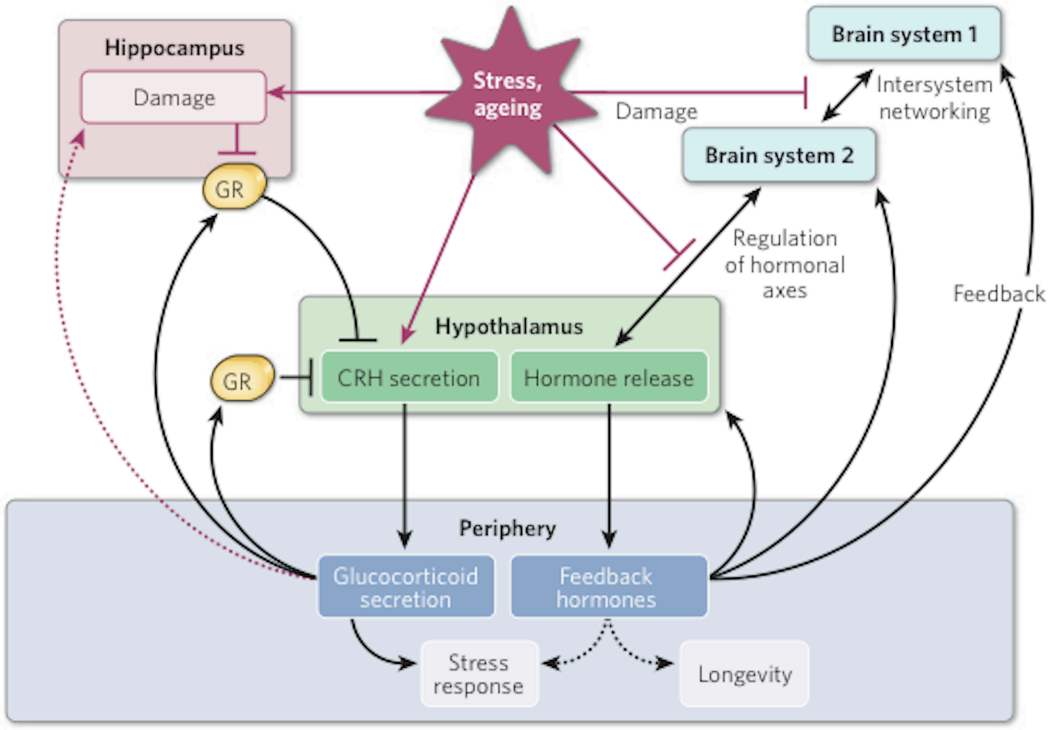


Figure 1.9. The brain and endocrine system as a potential regulator of organismal ageing.

The ageing of the brain may be coordinated with the ageing of organ systems through hormonal feedback circuits. Stressors induce hypothalamic production of corticotrophin-releasing hormone (CRH), leading to glucocorticoid release from the adrenal glands. The hippocampus senses glucocorticoid concentration through the glucocorticoid receptor (GR) resulting in feedback inhibition of release. Chronically elevated glucocorticoid levels during ageing may be detrimental to hippocampal function,

potentially setting up a spiral of hormonally mediated hippocampal decline. The right hand side of the diagram shows a general mechanism contributing to the decline of other functional systems in the brain, for example the IGF system. Reproduced with permission from (68).

1.14 Summary of brain and endocrine frailty

Cumulative ROS mediated DNA damage in post-mitotic neuronal cells may reduce the expression of selectively vulnerable genes leading to impaired synaptic plasticity, protein transport, mitochondrial function and neuronal survival that manifests as the cognitive decline of ageing (75). Cumulative age-related microglial damage leading to microglial priming may cause an abnormal response to local and systemic inflammation, with microglial overactivity following relatively minor stressor events causing accelerated neurotoxicity. Brain ageing in the hypothalamus and hippocampus may be a potential regulator of organismal ageing, through abnormal neuroendocrine homeostasis and impaired organ physiology. Impairments in glucocorticoid and IGF-1 homeostasis can potentiate neurotoxicity and may precipitate a spiral of progressive neurological and organismal decline. This progressive decline may manifest clinically as an increased risk of developing delirium in response to minor stressor events, worsening cognitive impairment and dementia.

1.15 The frail immune system

The competence of the immune system is reduced with age and is characterised by an age-related decline in immune stem cell lineages and an abnormal inflammatory response (22). Oxidative DNA damage to stem cells, mitochondrial dysfunction and telomere shortening are all considered to contribute to age-related immune senescence (22, 109). Significant changes in haematopoetic stem cells (HSCs) are observed, with a functional reduction in regenerative capacity and reduced output of B and T lymphocytes. In contrast, stem-cell derived neutrophil and macrophage numbers are increased, but the phagocytic ability of neutrophils and macrophages is reduced (22).

There is accumulating evidence to support the hypothesis that the senescent immune system has an important role in the pathophysiology of frailty. This appears to be principally through an abnormal inflammatory response that is constitutively active at a low-grade level, inappropriately hyper-responsive to inflammatory stimuli and persistently active for a prolonged period following removal of the initial inflammatory stimulus.

1.15.1 Inflammation

Inflammation is a protective immune response that is triggered by conditions such as infection and tissue injury, including ischaemia, hypoxia, trauma and physical/chemical injury (110-112). Inflammation is

designed to rid the organism of noxious stimuli and pathogens and hence restore physiological homeostasis; the absence of an adequate inflammatory response would lead to multiple deleterious outcomes, including unchecked infections and absence of wound healing (111). However, if the inflammatory response is not tightly regulated, chronic ROS mediated molecular and cellular damage may occur, accelerating cellular senescence and organismal ageing. A brief review of the inflammatory pathway will help identify the important mechanisms that are associated with frailty.

1.15.2 The inflammatory pathway

When considering the inflammatory pathway, it is helpful to distinguish between inducers, sensors, mediators and effectors of inflammation (110).

1.15.2.1 Inducers of inflammation

Inducers of inflammation are the exogenous and endogenous signals that initiate the inflammatory response. Exogenous signals can induce an acute inflammatory response either directly, in the case of some microbial pathogens, or through the effects of microbial virulence factors on host tissue cells, for example Gram-positive bacterial exotoxins (110). Non-microbial exogenous inducers include allergens, foreign bodies and toxins.

Endogenous inducers of acute inflammation are signals produced by stressed, damaged and malfunctioning tissues that are, under normal circumstances, confined to the cell. Cellular damage can result in the transmembrane release of a large number of inflammatory inducers including ATP, potassium ions and calcium binding proteins (110). These inducers can both directly induce the inflammatory response and activate pain receptors (nociceptors) which relay information to the central nervous system; a key regulator of the inflammatory response (113, 114). Furthermore, damage to vascular endothelium allows plasma proteins to access the extracellular space and facilitates direct activation of the inflammatory response (115).

A further series of endogenous inducers include monosodium urate and calcium pyrophosphate crystals, which precipitate in joints and periarticular tissues to cause gout and pseudogout. These crystals are detected by macrophages and treated in the same manner as foreign bodies to precipitate an inflammatory response (110).

High-density and low-density lipoprotein molecules can induce an inflammatory response following oxidation by macrophage-generated ROS, and ROS dependent oxidation of extracellular matrix components can also induce inflammation (110).

1.15.2.2 Sensors of inflammation

Exogenous and endogenous inducers of inflammation are detected by a series of sensors, which include receptors such as IgE and the Toll-like receptors that are present on the surface of immune cells, including macrophages, B lymphocytes and mast cells (110).

1.15.2.3 Mediators of inflammation

Once detected by sensors, inflammatory inducers trigger the generation of multiple mediators of inflammation, which can ultimately alter the function of tissues and organs. Derived from plasma proteins or produced by specialised leukocytes and tissue cells, the inflammatory mediators can be classified into seven groups; vasoactive amines (e.g. histamine and serotonin), vasoactive peptides (e.g. substance P), complement components (e.g. C3a, C4a, C5a), lipid mediators (e.g. eicosanoids and platelet activating factor), cytokines (e.g. TNF α, interleukin-1 (IL-1), interleukin-6 (IL-6)), chemokines and proteolytic enzymes (e.g. elastin, proteinases) (110, 111). Inflammatory mediators can also alter the production of other mediators, for example TNF activates cells to increase expression cytokines (e.g. IL-1) and eicosanoids.

1.15.2.4 Effectors of inflammation

The effectors of inflammation are the cells and tissues that are affected by the inflammatory mediators. Some mediators (e.g. TNF, IL-1) exert

their effects on virtually all cells, but the effects may be different depending on cell type (110). Although outcomes such as exudate formation through changes to endothelial cells and promotion of leukocyte migration are perhaps more obvious effects of inflammatory mediators, many mediators have equally important effects on the neuroendocrine system and metabolism (97, 110).

Acute inflammation is classically associated with infection and tissue injury. Localised chronic inflammation can occur as a result of, for example, chronic infection and autoimmune disease. Systemic chronic inflammation occurs in a variety of diseases, including type 2 diabetes and cardiovascular disease (110). Although the physiological purpose of the acute inflammatory response following an infective trigger has been well characterised (i.e. to remove infection), the physiological purpose of systemic chronic inflammation is less well understood but appears to be associated with a more generalised physiological homeostatic imbalance (110).

1.15.3 Regulation of the inflammatory response

Adequate regulation of the magnitude of the inflammatory response is essential; an insufficient inflammatory response can lead to immunodeficiency and overwhelming infection, an excessive response can lead to chronic inflammatory damage and autoimmune disease. In certain situations, such as septic shock, the inflammatory response can

initiate a more detrimental outcome than the initial stimulus (116). Through a critical homeostatic inflammatory feedback reflex, a number of checkpoints exist to precisely regulate the targeted destruction and assisted repair that characterise the inflammatory response (117). This precise regulation involves a complex interaction between multiple local and circulating pro- and anti-inflammatory mediators that are reflexively monitored and adjusted by the nervous system (116).

1.15.3.1 Pro-inflammatory mediators

An acute inflammatory response that is triggered by infection or tissue injury results in the delivery of plasma proteins (e.g. antibodies) and leukocytes to the site of infection or injury. The response is initiated by tissue macrophages and mast cells, which produce a wide range of inflammatory mediators that promote increased tissue blood flow, increased vascular permeability to plasma proteins and neutrophil migration (110, 111).

Tumour-necrosis factor (TNF) is an important pro-inflammatory mediator that is required for both local and systemic inflammation (111). Produced by activated macrophages, local increases in TNF lead to detectable signs of inflammation (redness, heat, swelling) whereas systemic increases in TNF can mediate tissue injury by depressing cardiac output, inducing microvascular thrombosis and causing increased capillary permeability (116).

Neutrophils that are activated by direct contact with pathogens or inflammatory cytokines release ROS and potent enzymes in an attempt to kill the invading agent. As these ROS and enzymes do not discriminate between invading agents and host tissues, some damage to host cells is inevitable (117).

1.15.3.2 Anti-inflammatory mediators

Although the inflammatory response functions as a defense mechanism, the unregulated generation of pro-inflammatory mediators can cause injury to healthy cells (118). To regulate inflammation, cell-cell interactions between activated leukocytes and tissue cells promote the generation of a series of anti-inflammatory mediators that limit the inflammatory response and prevent the dissemination of pro-inflammatory mediators into the systemic circulation (116). Anti-inflammatory cytokines, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), inhibit the release of pro-inflammatory mediators such as TNF-α (119). Anti-inflammatory hormones including adrenal glucocorticoids, adrenaline and α-melanocyte stimulating hormone (α-MSH) also inhibit inflammatory cytokine synthesis. Local anti-inflammatory agents including spermine, prostaglandin E2 and acute phase proteins inhibit macrophage activation and cytokine synthesis (116, 118). These anti-inflammatory mediators are generated hours to days after the initial inflammatory stimulus.

Experimental impairment of these anti-inflammatory responses in animals can cause significant detriment. Loss of adequate glucocorticoid response via hypophysectomy or adrenalectomy causes an amplified response to endotoxin and overexpression of TNF; IL-10 deficiency leads to development of chronic inflammatory bowel disease; pharmacological spermine antagonism increases local TNF activity and amplifies the inflammatory response (116, 118, 120, 121). Loss of these anti-inflammatory mechanisms converts a protective, self-limiting inflammatory response into an unregulated, excessive, potentially damaging systemic response (116).

Although fundamentally protective, inadequate regulation of inflammation can lead to persistent molecular and cellular damage. A diagrammatic overview of inflammatory response triggers and their associated potential physiological and pathological outcomes is provided in figure 1.10.

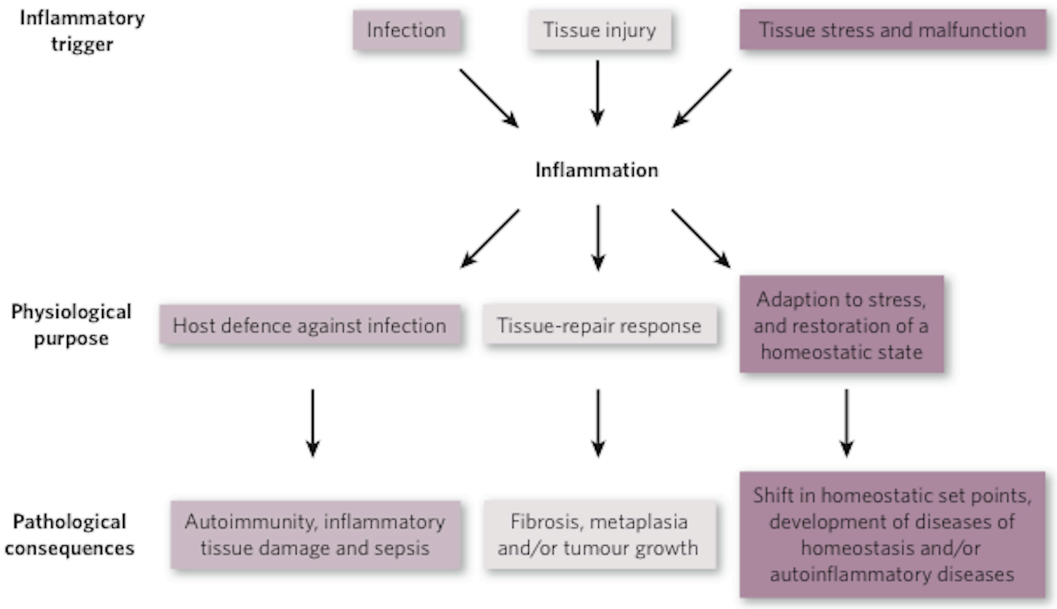


Figure 1.10. Triggers, physiological purposes and pathological outcomes of inflammation.

Depending on the trigger, the inflammatory response has a different physiological purpose and pathological consequence. Reproduced with permission from (110).

The senescent immune system may function adequately in the quiescent state but fail to respond appropriately to the stress of acute inflammation, including the common precipitants of infection and tissue injury (22). A low grade inflammatory state is common in older people and activated lymphocytes and monocytes of healthy older people produce greater levels of the pro-inflammatory cytokine IL-6 (122-124). Inflammation has been implicated as having an important pathogenic role in many age-related diseases, including Alzheimer's disease, atherosclerosis, heart failure, osteoporosis and osteoarthritis (117, 125-127). Inflammation has

also been implicated in the pathophysiology of sarcopenia, an important component of the frailty phenotype (128, 129).

1.15.4 Inflammation and frailty

There is substantial evidence to indicate that inflammation has a key pathophysiological role in frailty. A large prospective cohort study involving 5201 participants reported an association between C-reactive protein (CRP) and incident frailty as defined by the Fried criteria (130). In a multivariate analysis adjusted for important covariates, every standard deviation increment in baseline CRP increased the five year incidence of frailty by 18% (Hazard Ratio, HR 1.18, 95% confidence interval, CI, 1.04 - 1.34).

A recent UK case-control study that included 101 participants reported results from a multivariate analysis demonstrating that TNF-α, IL-6 and CRP were independently associated with increasing frailty, defined using Fried criteria, Frailty Index and functional status. Increasing frailty was negatively associated with albumin using all three definitions of frailty (131).

A further cross-sectional study reported an independent association between increased white blood cell (WBC) counts, IL-6 and frailty in 558 older women (132). Those in the top tertile for WBC measurements had an odds ratio (OR) of 3.15 (95% CI 1.34 - 7.41) for frailty. The

corresponding OR for IL-6 was 2.81 (95% CI 1.19 - 6.64). Two additional studies that pre-dated current definitions of frailty reported that increased IL-6 and CRP were associated with increased risk of functional disability and death in community dwelling older people (133, 134).

The molecular mechanisms underlying increased levels of inflammatory cytokines in frailty are beginning to be elucidated. CXC chemokine ligand-10 (CXCL-10) is a potent pro-inflammatory mediator that is produced by many types of immune cells in response to stimuli including lipopolysaccharide (LPS) and interferon-γ (IFN-γ) to stimulate neutrophil and lymphocyte activation (135). CXCL-10 levels increase with age, but in two recent cross-sectional studies older people identified as frail using the Fried criteria had higher levels of unstimulated and LPS-stimulated monocyte CXCL-10 expression when compared to age matched controls (136, 137). There was also a strong association between CXCL-10 and IL-6 in the frail older participants (136).

1.15.5 The frail brain and impaired endocrine regulation of the inflammatory response

The brain and nervous system play a central role in regulation of the inflammatory response by both sensing and responding to inflammation through circulating humoral and direct neural mechanisms. Circulating inflammatory cytokines including TNF gain nervous system access through areas of the brain in which a blood-brain barrier is absent, and

stimulate hypothalamic-pituitary (HP) responses to inflammation, including fever and anorexia (116). Afferent sensory and pain fibres transmitted from peripheral tissues via the vagus and other nerves can also activate HP inflammatory responses, notably at levels of inflammation below that required for circulating cytokine activation. Furthermore, cells of the immune system can produce neuropeptides such as endorphins and neurotransmitters including acetylcholine to provide additional input to the nervous system (116).

Detection of inflammation by the nervous system leads to activation of the hypothalamic-pituitary-adrenal (HPA) axis and stimulation of anti-inflammatory glucocorticoid release, leading to suppression of further inflammatory cytokine release (138). In addition to regulation of the HPA axis, the nervous system modulates the inflammatory response directly via efferent sympathetic and parasympathetic nerve activity. Adrenaline and noradrenaline mediated afferent sympathetic activity can induce macrophage inhibition, suppression of inflammatory cytokine synthesis and increases in the anti-inflammatory cytokine IL-10 (139, 140). Acetylcholine mediated vagal afferent parasympathetic innervation induces similar macrophage inhibition and suppression of TNF and other cytokine production (116). Vagus nerve activity is also relayed to other areas of the brain, including the hypothalamus, to increase activation of the HPA axis.

The wiring of this complex reflex mechanism is illustrated diagrammatically in figure 1.11.

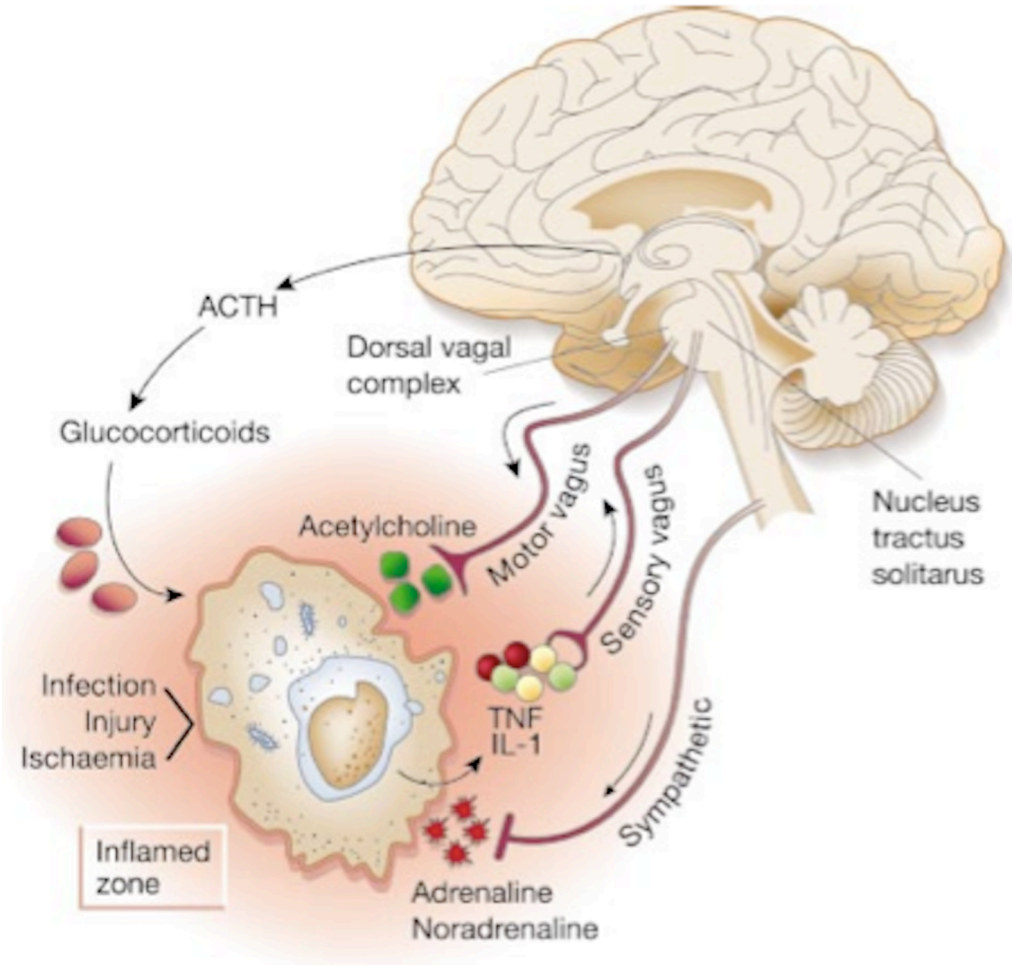


Figure 1.11. The inflammatory reflex.

Inflammatory products produced in damaged tissues activate afferent signals that are relayed to the nucleus tractus solitarius. Subsequent activation of vagus efferent activity inhibits cytokine synthesis through the cholinergic anti-inflammatory pathway (the inflammatory reflex). Information can also be relayed to the hypothalamus and the dorsal vagal complex to stimulate the release of ACTH, thereby activating the humoral anti-inflammatory pathway.

Activation of the sympathetic outflow can increase local concentrations of catecholamines, which can suppress inflammation further. ACTH, adrenocorticotrophic hormone; TNF, tumour necrosis factor; IL-1, interleukin-1. Reproduced with permission from (116).

1.15.6 The hypothalamic-pituitary-adrenal (HPA) axis, cortisol and frailty

Inflammatory mediators activate the HPA axis to produce cortisol, which has multiple downstream effects including feedback inhibition of the inflammatory response, increased metabolism and altered brain function characterised by increased hippocampal activity (141). Supported by a large meta-analysis, there is a growing consensus that reactivity of the HPA to inflammatory stimuli is significantly increased with age (142).

Demonstration of persistence of elevated cortisol levels in frail older people following inflammatory and adrenal challenge would provide further evidence to support the biologically plausible potential role of an abnormal inflammatory reflex in the development of frailty.

1.15.7 Ageing and anaemia

Anaemia is common in older people, becoming increasingly prevalent with advancing age, and is associated with vulnerability to adverse

outcomes, including an independent increase in mortality risk (143, 144). Anaemia has been independently associated with increased risk of frailty in one cross-sectional analysis that included 670 older participants, but the possibility of residual confounding despite adjustment for important covariables was reported (145).

1.16 Frail skeletal muscle - sarcopenia

Sarcopenia is characterised by progressive loss of skeletal muscle mass, strength and power and is considered to be a key component of frailty (146, 147). Under normal circumstances, muscle homeostasis is maintained in a delicate balance between new muscle cell formation, muscle cell hypertrophy and muscle cell protein loss. This delicate balance is coordinated by the brain, endocrine system and immune system and is influenced by nutritional factors and senescent physical activity. The adverse molecular, neural, endocrine and immune components of frailty have the potential to upset this delicate homeostatic balance and accelerate the development of sarcopenia.

Muscle strength and power are required for the critical basic mobility skills of getting out of bed, standing up from a chair, walking a short distance and getting off the toilet (148). When the ability to perform these critical skills is impaired, an older person is at risk of immobility, causing further loss of muscle mass, risk of falls and activity limitation. Indeed, sarcopenia has been independently associated with increased falls risk

(OR 2.6, 95% CI 1.42 - 4.73) and development of disability (OR 3.7, 95% CI 1.4 - 10.0).

Muscle power, the product of muscle torque and movement, appears to be more closely associated with functional physical performance than static muscle strength and declines more rapidly with age (149). Muscle power may therefore have greater utility as a measure of physiological impairment and functional deficit. As muscle strength and power do not depend entirely on muscle mass, and the relationship is non-linear, recent consensus criteria recommend using the presence of low muscle mass and either low muscle strength or low physical performance to diagnose sarcopenia (147). Observational studies have reported losses of muscle strength and power of between 1-3% per annum in older people, with even greater losses observed in the oldest old (150).

A schematic representation of the interaction of these multiple mechanisms is provided in figure 1.12. The complex interaction between these multiple contributory factors will be considered in greater detail.

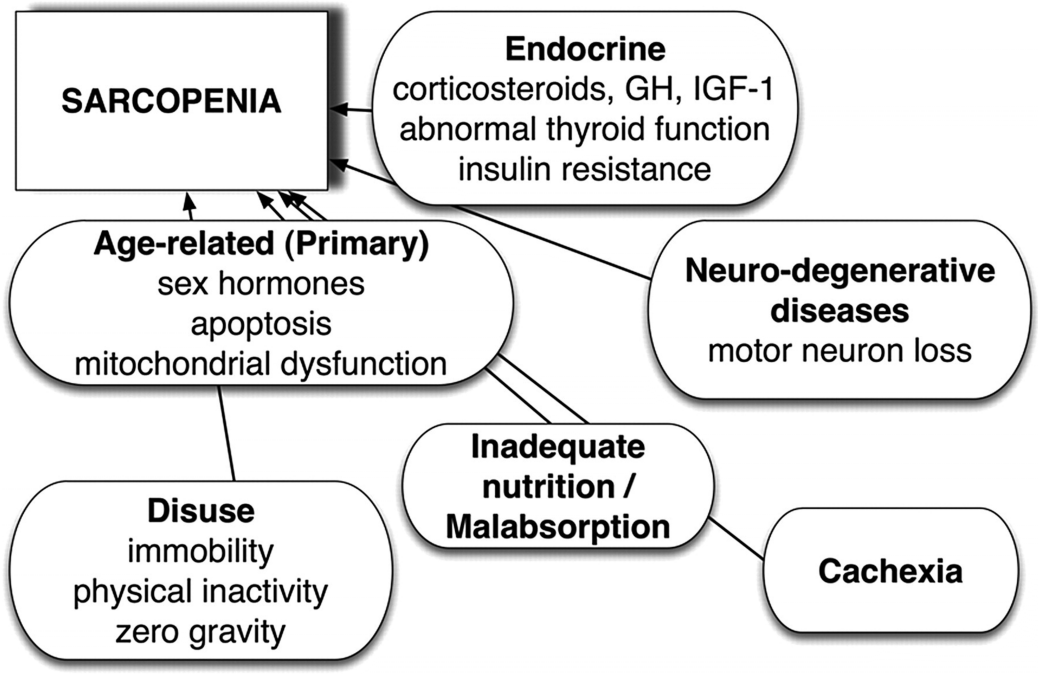


Figure 1.12. Mechanisms of sarcopenia.

Reproduced with permission from (147)

1.16.1 Skeletal muscle stem cells

Skeletal muscle fibres (myocytes) are syncytia derived from the fusion of multiple individual embryonic cells and therefore contain multiple nuclei (111). These post-mitotic cells are supported by a stem cell population located beneath the myocyte cell membrane that are responsible for generating new muscle fibres in response to injury (151). Muscle stem cells, or satellite cells (SCs), are activated by stimuli that alter the microenvironment, including exercise and injury. Interstitial cells, immune cells and vascular cells are activated to secrete multiple factors that promote SC growth, including endothelial derived growth factors such as Vascular Endothelial Growth Factor (VEGF) and IGF-1 (151). SCs are

also influenced by neural factors and are also activated in response to neuromuscular denervation (152).

Ageing SCs demonstrate an impaired capacity for differentiation and regeneration and are more susceptible to apoptosis (153, 154). Diminished regeneration is most apparent after muscle injury (22). Although absolute numbers of satellite cells are reduced in animal models of ageing, human skeletal muscle does not reliably demonstrate a similar reduction, and changes to the SC microenvironment are considered to be more important (155). This is supported by the observation that an adequate surrounding microenvironment can restore the function of aged SCs (22, 151). These age-related changes to the microenvironment are illustrated schematically in figure 1.13.

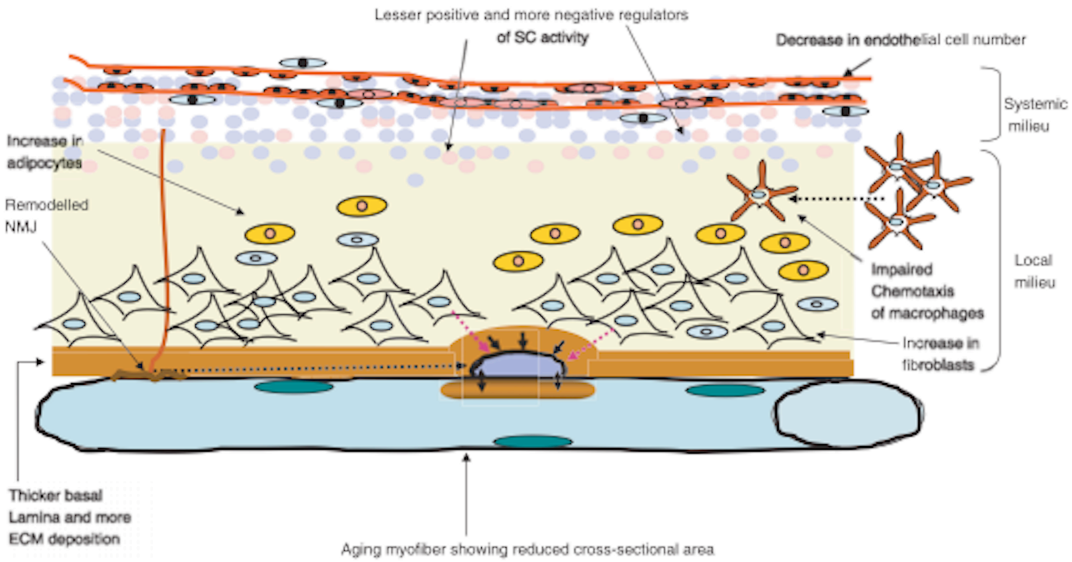


Figure 1.13. Schematic illustration of the satellite cell (SC) niche in aged skeletal muscle.

Age-related changes to endothelial cells, interstitial cells, and immune cells, a thickened basal lamina and remodelling of the neuromuscular junction all contribute to reduced activation and proliferation of SCs. Reproduced with permission from (151).

1.16.2 Oxidative damage and sarcopenia

There is accumulating evidence to support a central role of increased oxidative stress and mitochondrial DNA damage in the development of sarcopenia. Increased muscle protein carbonyl levels, indicators of oxidative stress, along with evidence of increased mitochondrial DNA damage in muscle samples from older people have been reported (156, 157). Furthermore, a 2007 cross-sectional study involving 672 women aged 65 and older identified that higher levels of carbonylated proteins were associated with reduced grip strength, an indicator of sarcopenia (146).

1.16.3 Reduced muscle mitochondrial function

Muscle is a tissue with high metabolic activity and is adversely affected in a number of inherited mitochondrial disorders (68). Mitochondrial DNA mutations accumulate with age and have been associated with mitochondrial dysfunction, apoptosis and sarcopenia in animal models (158). Mitochondrial DNA polymorphisms have also been independently

associated with grip strength, a measure of sarcopenia, in older adults (35).

1.16.4 Muscle protein breakdown and sarcopenia

All cellular proteins are continually being degraded and replaced. The rate of turnover is dependent on cell type and in muscle cells the majority of proteins are replaced every one to two weeks (48). The homeostatic balance between protein synthesis and breakdown is critical and tight regulation of this process is necessary as even a small change to protein synthesis or breakdown can result in a significant loss of body mass (48). Muscle protein breakdown pathways are influenced by components of the inflammatory reflex and endocrine factors.

1.16.4.1 The ubiquitin-proteasome pathway

The ubiquitin-proteasome (UP) pathway is of key importance in the breakdown of muscle protein leading to the muscle wasting that is observed in many catabolic states, including malnutrition, chronic inflammation and malignancy. Levels of ubiquitin conjugates in muscle cells and ubiquitin mRNA increase during these conditions, indicating a coordinated response that promotes muscle wasting during periods of stress to provide amino acids as both a direct muscle energy source and a substrate for hepatic gluconeogenesis (159). A similar ubiquitin mediated response occurs following muscle denervation, leading to

muscle wasting (159). The activity of the UP pathway is influenced by both inflammatory and endocrine factors.

1.16.4.2 Lysosomal pathways

Skeletal muscle cells contain few lysosomes and they are not considered to contribute significantly to overall proteolysis (160).

1.16.5 Inflammation and sarcopenia

There is evidence that inflammation is associated with the development of sarcopenia. A cross-sectional sample of 680 people participating in a prospective cohort study identified that IL-6 was independently associated with sarcopenia following a multivariate analysis that adjusted for important confounding variables (128).

1.16.5.1 Inflammation and increased proteolysis

Inflammatory cytokines such as IL-6 and TNF can activate the UP pathway leading to muscle proteolysis. In addition to the generation of amino acids for energy, activation of UP by IFN appears to facilitate the cleavage of small antigenic peptides that have the potential to enhance the specificity of the immune response (161). This response, which under normal circumstances serves a fundamentally protective physiological purpose, may become pathological in the presence of an overactive, insufficiently regulated inflammatory response that characterises frailty.

Functionally debilitating loss of muscle mass and strength may therefore be the consequence of an overactive inflammatory response in the presence of frail skeletal muscle. This may be detected clinically as a significant deterioration in the basic mobility skills of standing from a chair, getting out of bed, walking to the toilet, and climbing stairs, which may manifest as measurable functional impairment.

1.16.6 Endocrine components of sarcopenia

1.16.6.1 IGF-1

IGF-1 is considered to play a key role in the maintenance of muscle strength. Although systemic GH dependent IGF synthesis by the liver may have a role, the autocrine and paracrine effects of GH-independent local IGF-1 production by muscle cells in response to changes in the microenvironment are believed to be of particular importance (101).

IGF-1 acts to increase muscle strength by promoting increased myocyte number, activating muscle cell hypertrophy and inhibiting muscle protein breakdown. Increased myocyte number is considered to be through promotion of SC proliferation and differentiation (151). Activation of muscle cell hypertrophy is through an IGF-mediated direct and indirect cascade of kinase enzymes and the TOR signalling pathway (162). Inhibition of muscle protein breakdown is facilitated through downregulation of components of the UP pathway (163).

Evidence to support an association between IGF-1 and sarcopenia has been provided by a prospective cohort study involving 558 participants, which reported results from a multivariate analysis that identified a statistically significant association between IGF-1 levels and sarcopenia (128).

1.16.6.2 Glucocorticoids

Glucocorticoids (GCs) stimulate muscle protein breakdown by upregulating expression of mRNA encoding for UP subunits leading to increased proteolysis (50, 164). GCs also act to inhibit protein synthesis. The chronic elevation and inadequate feedback regulation of GCs in frailty has the potential to promote the accelerated, sustained development of sarcopenia.

1.16.6.3 Testosterone

Testosterone supplementation can increase skeletal muscle mass in both young and older males, principally through promotion of myofibre hypertrophy and increased SC number (165). However, a recent randomised controlled trial of testosterone supplementation involving 209 older participants with limitations in mobility and low serum testosterone was terminated early due to safety concerns. Although the intervention group demonstrated significant improvements in arm and leg strength compared to the placebo group, a higher rate of adverse cardiovascular

and respiratory events in the intervention group led to a recommendation from the data and safety monitoring board that the trial be discontinued (166).

1.16.7 Neuromuscular components of sarcopenia

Ageing skeletal muscle demonstrates impaired neuronal innervation characterised by alterations in spinal cord motor neurons and reduced neuromuscular junction synapse formation. These changes are considered to contribute to the development of sarcopenia via reduced action potential generation leading to reduced force of muscle contraction and changes to stimulation of neurotropic factors, including nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-1).

Recent evidence indicates that impaired neuromuscular activation may be more pronounced in older people who are mobility limited compared to those who are not limited (149). Changes to the nervous system, including loss of cortical projections to spinal motor neurons, reduced inhibition between cerebral hemispheres and reduced corticospinal pathway excitability may underlie this impaired neuromuscular activity (167-169).

1.17 Nutrition and frailty

Weight loss is considered to be one of the core components of frailty and has been associated with adverse outcomes including increased risk of infection, admission to long-term care and mortality (3, 170-172). However, the multiple potential confounding variables that require consideration in observational studies of nutrition and frailty mean that there is ongoing uncertainty regarding whether nutrition is a true independent risk factor for adverse outcomes.

A complex interaction between inflammatory mediators and the hypothalamus, along with changes in leptin and neuropeptide Y are likely to be important factors in the pathophysiology of weight loss in older age (173, 174).

1.17.1 Inflammation and nutrition

Inflammation is associated with anorexia and catabolism of skeletal muscle and adipose tissue (173). This can be detected clinically as weight loss, and may be of particular functional importance in the presence of pre-existing sarcopenia. Inflammatory cytokines including IL-1, IL-6 and TNF are considered to be key pathophysiological mediators of anorexia and tissue catabolism in acute and chronic inflammation (173, 175).

Inflammation associated anorexia is a fundamentally protective mechanism to divert resources away from food seeking behaviour and digestion so that energy can be directed towards generating a vigorous immune response. The brainstem, hippocampus, amygdala and hypothalamus are key components of a complex neuronal network that regulates the feeding response. Although peripheral sensory nerves and inflammatory cytokines provide direct and indirect input into these brain areas, and are considered to be important moderators of the feeding response, the precise neuronal mechanism for induction of inflammation associated anorexia is currently unknown (176).

1.17.2 Leptin and frailty

Leptin is a circulating peptide hormone with a number of important roles including regulation of energy homeostasis and metabolism (177). It is manufactured by adipose tissue and, under certain conditions, skeletal muscle and gastric parietal cells (178). Leptin signals the nutritional status of the body to the brain through stimulation of receptors located in the hypothalamus and limbic system. Hypothalamic stimulation moderates the production of a series of neuropeptides that regulate appetite, including neuropeptide Y, resulting in reduced food intake. Stimulation of the limbic system moderates motivation and reward pathways associated with feeding (177).

A 2008 cross-sectional study involving 140 participants investigated the association between inflammation, leptin and frailty (174). The frailest participants displayed features of cachexia, with significantly lower BMI when compared to those who were less frail. Leptin levels were correspondingly lower in the most frail and inflammatory markers were significantly increased. Pressure ulcers were more common in those who were most frail. Although participant numbers were relatively small, this study provides support for a biological mechanism of weight loss in frailty. The combination of a frail brain, frail immune system and frail endocrine system may lead to weight loss and cachexia through an inability to regulate an overactive inflammatory response in association with impaired hypothalamic endocrine control.

1.17.3 Nutritional intervention in frailty

There is a paucity of high quality randomised controlled trials (RCTs) investigating nutritional intervention in frailty. One RCT that investigated the effects of exercise and nutritional supplementation in 100 frail older people living in long-term care reported that nutritional supplementation had no effect on muscle strength, gait velocity, stair climbing activity or physical activity (179). A 2003 Cochrane review of nutritional interventions for preventing and treating pressure ulcers in older hospital patients, an at risk group who are more likely to be frail, reported that it was not possible to draw any firm conclusions due to a general absence of trials of high methodological quality (180). Furthermore, calorific

restriction has been observed to extend lifespan in a number of organisms and appears to reduce organ injury following inflammation in animal models (181). It is possible that the weight loss and cachexia that are observed in frailty result from a hyperactive, inadequately regulated inflammatory response and interventions to target these adverse biological mechanisms may have potential to improve the adverse nutritional profile of frailty.

1.18 Social vulnerability and frailty

Multiple social vulnerability factors including neigbourhood deprivation, social isolation and poor socioeconomic status have been associated with important adverse health outcomes including depression, cognitive impairment, admission to long-term care and death (182-184). More recently, evidence to support an association between social vulnerability and frailty has been reported in two large observational studies (5, 185).

In order to operationalise social vulnerability according to a deficit accumulation approach, investigators from the Canadian Study of Health and Ageing (CSHA) analysed data from 10,263 study participants aged 65 and over. The social vulnerability index included items such as communication, social support, social engagement and socioeconomic status. Social vulnerability increased with age and was greater in women. A moderate correlation between frailty and social vulnerability was reported. Both frailty, identified using the FI, and social vulnerability

independently contributed to increased risk of mortality suggesting that, although related, frailty and social vulnerability are likely to be distinct (5).

A 2009 cross-sectional analysis of data from 4818 participants in the English Longitudinal Study of Ageing (ELSA) identified an independent association between individual socioeconomic status, neighbourhood deprivation and frailty. In a multivariate analysis adjusted for important potential confounding variables, lower individual wealth and greater neighbourhood deprivation were independently associated with frailty, identified using the FI (185).

1.18.1 Potential biological effects of social vulnerability

The relationship between frailty and social vulnerability is complex, but there is evidence to support a potential association between psychosocial stress and accelerated cell ageing through molecular, epigenetic and neuroendocrine mechanisms (186). Environmental stressors trigger a series of neurological and endocrine responses designed to preserve homeostasis (187). The most common responses involve activation of the autonomic nervous system and HPA axis, and the frail brain and endocrine system may be increasingly vulnerable to an overactive, sustained GC response following environmental stress (188). Although no causative relationship can be inferred, a 2008 analysis of cross-sectional data from a cohort of 8,643 older people in the UK reported a

socioeconomic gradient in IGF-1 levels and markers of inflammation in older people (186).

Recent studies have demonstrated an association between chronic psychosocial stress, levels of cellular oxidative stress and shorter telomere length (189, 190). The activation of autonomic and neuroendocrine systems, with an associated glucocorticoid driven increase in ROS, may accelerate telomere damage, p53 activation and cell senescence (22, 190).

1.18.2 Epigenetic factors

It has been hypothesised that epigenetic programming early in life may influence the late-life stress response (61). There is preliminary evidence that social adversity in early life is associated with increased levels of DNA methylation in hippocampal neurons (61). There is ongoing uncertainty regarding the persistence and importance of early epigenetic changes throughout life, the reversibility of these changes and the role of late-life epigenetic mechanisms that result from social adversity in older age. Investigation of the relationship between epigenetic mechanisms, social vulnerability and frailty will potentially provide insight into how social adversity and biological health are intrinsically related. Greater insight into these mechanisms will further understanding and inform the future development of interventions to improve the adverse health outcomes of social vulnerability in frail older people.

1.19 Consequences of frailty

Bernard Isaacs contended that, if you look closely enough, all common problems in older age can be traced back to one or more of the four 'geriatric giants', namely intellectual impairment, instability, immobility and incontinence (191). Frailty, and markers of frailty, have been independently associated with all four of these giants (3, 94, 95, 192). Frailty is also independently associated with increased risk of hospitalisation, admission to long-term care and death (3, 11). Understanding the biological causative mechanisms of frailty provides deeper insight into these adverse consequences.

Characterised by vulnerable hippocampal neurons and primed microglia, a frail brain that is unable to maintain homeostatic control of an inappropriate inflammatory response originating from a frail immune system may be at risk of rapid intellectual impairment in the form of delirium. Accelerated neuronal damage may subsequently increase the risk of further cognitive decline and dementia. The combination of a frail brain and frail muscles may result in a cumulative impairment of coordination and strength, jeopardising successful completion of the complex task of walking, resulting in instability and falls. Frail skeletal muscle, with reduced regenerative capacity, is at risk of a temporary or permanent loss of strength leading to immobility and disability, particularly following the persistent catabolic endocrine state that characterises the

frail inflammatory reflex. Impaired neuronal control and reduced ability to walk to the toilet resulting from the combination of a frail brain and frail muscles may cause or exacerbate incontinence.

Delirium and falls are common precipitants for hospital admission. Behavioural problems associated with dementia and the onset of incontinence are common reasons for admission to long-term care. A deeper understanding of the biological mechanisms of frailty provides clearer insight into the contribution of frailty to the common problems and adverse health outcomes that are frequently observed in older age.

1.20 Frailty, disability and comorbidity

The relationship between frailty, disability and comorbidity (defined as the presence of two or more chronic diseases) is complex. There is emerging agreement that, whilst frailty, disability and comorbidity are closely related and exhibit significant overlap (193), they are not synonymous. Therefore, as frailty develops with multisystem physiological decline, it is possible that an individual may be phenotypically and measurably frail in the absence of comorbidity. However, the effects of a single disease that is severe, the presence of subclinical disease or the presence of undiagnosed disease adds further complexity.

Disability in older age can be measured using standardised instruments that assess activities of daily living (ADL), for example the Barthel Index

(194). Disability in older age can develop progressively (e.g. as a result of frailty) or catastrophically (e.g. as a result of stroke or hip fracture). Results from a cohort of 6640 older people suggest that approximately 50% of disability in older age develops progressively and 50% develops catastrophically (195). The contribution of physiological frailty to the development of disability in older age is likely to be considerable.

1.21 Frailty, disability and future population projections

1.21.1 The ageing population

A gain in life expectancy (LE) of approximately 30 years was recorded over the course of the 20th century and a linear increase in LE looks set to continue throughout the 21st century (196). LE is an estimate of mean expected life span (197). Period life expectancy (PLE) provides an estimate of the mean LE at a given age (see table 1.2). Although important measures, LE and PLE provide no estimate of the proportion of life an individual can expect to remain in good health and free of disability.

Health expectancies measure both quality and quantity of life and divide LE into years of good health and years of ill health. Disability free life expectancy (DFLE) is one measure of health expectancy that provides an estimate of the number of years of life an individual can expect to be free of either a limiting long-term condition or disability (198).

	Period Life Expectancy (Years)	
Age (Years)	Male	Female
70	13.4	15.8
75	10.2	12.2
80	7.6	9.0
85	5.5	6.5
90	3.9	4.4
95	2.8	3.1
100	2.1	2.1

Table 1.2. 2005-2007 UK period life expectancy.

Source: National Statistics Website: www.statistics.gov.uk. Crown copyright material is reproduced with the permission of the Controller Office of Public Sector Information (OPSI)

1.21.2 Ageing and disability

The Measuring Health and Disability in Europe (MHADIE) consortium propose a definition of disability based on the World Health Organisation's (WHO) International Classification of functioning, disability and health (ICF). The MHADIE definition describes disability as "...a difficulty in functioning at the body, person, or societal levels, in one or more life domains, as experienced by an individual with a health condition in interaction with contextual factors" (199).

Older people can expect to remain independent and free of disability for the majority of the duration of their life expectancy (200, 201). Between the ages of 70-79, 73% of older people are estimated to be free from any disability and 93% are estimated to be independent for ADLs (201). Above the age of 80 the corresponding figures are 63% and 81%. Males aged over 80 can expect to remain in a disability free health state for 72% of their remaining life expectancy, with a corresponding figure for females of 64% (201).

1.21.3 Future projections

The above data suggest that the latter stages of life are likely to be associated with a period of disability. For accurate health and socioeconomic planning, it is of critical importance to determine whether gains in LE will be associated with improvements in HLE and DFLE. As frailty has a negative impact on health and well-being and is an independent risk factor for disability, prediction of the future prevalence of frailty is important. The development of interventions that improve the adverse health outcomes of frailty would have potential to improve HLE and DFLE. Although currently uncertain, it is plausible that any future changes in disability prevalence will be preceded by similar changes in frailty prevalence.

Three potential scenarios are projected for the future of HLE (202).

1. Compression of morbidity

LE and HLE gains are mirrored and the period of healthy life prior to death is increased. Health and social care costs (primarily in the form of long-term care) will potentially be reduced, although pension costs will continue to increase.

2. Expansion of morbidity

   Increase in overall LE is not mirrored in HLE gains. The period of ill health prior to death is extended. Substantial increases in health and social care expenditure are to be anticipated.

3. Dynamic equilibrium

   Modifications to disease progression resulting in a lower burden of severe levels of disability create a consequent reduction in severe disability and overall equilibrium in health and social care costs.

Current UK projections suggest that the increase in overall LE may not be mirrored by an increase in HLE. Between 1981 and 2004, LE increased at a faster rate than HLE (see figure 1.14). However, there is scope for optimism; between 2001 and 2004 there was a decrease in the time spent with a limiting illness or disability in both men and women in the UK. A decrease of 1 year was noted in men; a decrease of 0.5 years in women (203).

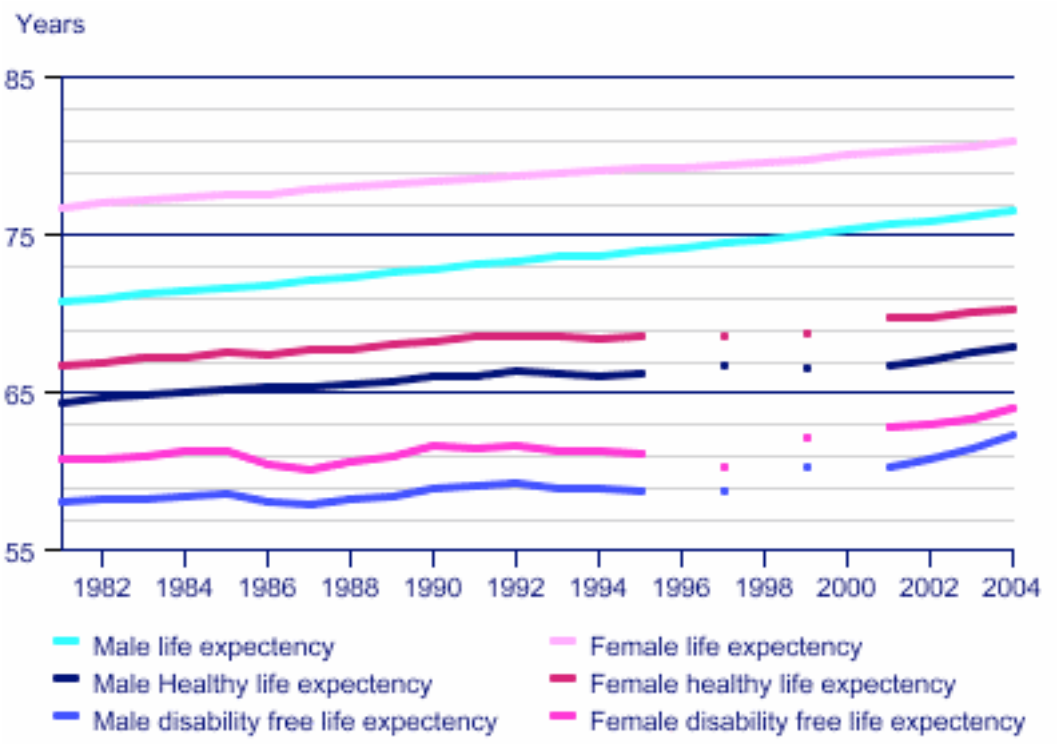


Figure 1.14. Life expectancy, healthy life expectancy and disability free life-expectancy, UK, 1981-2004.

Source: National Statistics Website: www.statistics.gov.uk. Crown copyright material is reproduced with the permission of the Controller Office of Public Sector Information (OPSI)

It is reassuring to note that there is also increasing international evidence to suggest that prevalence rates of disability in older age in Western populations are falling (196), with the caveat that this apparent fall may be due in part to an increase in the prevalence denominator. Data from the European Union (EU) for the period 1995-2003 show a degree of variation in trends in LE and DFLE across EU member states (figure 1.15) (204).

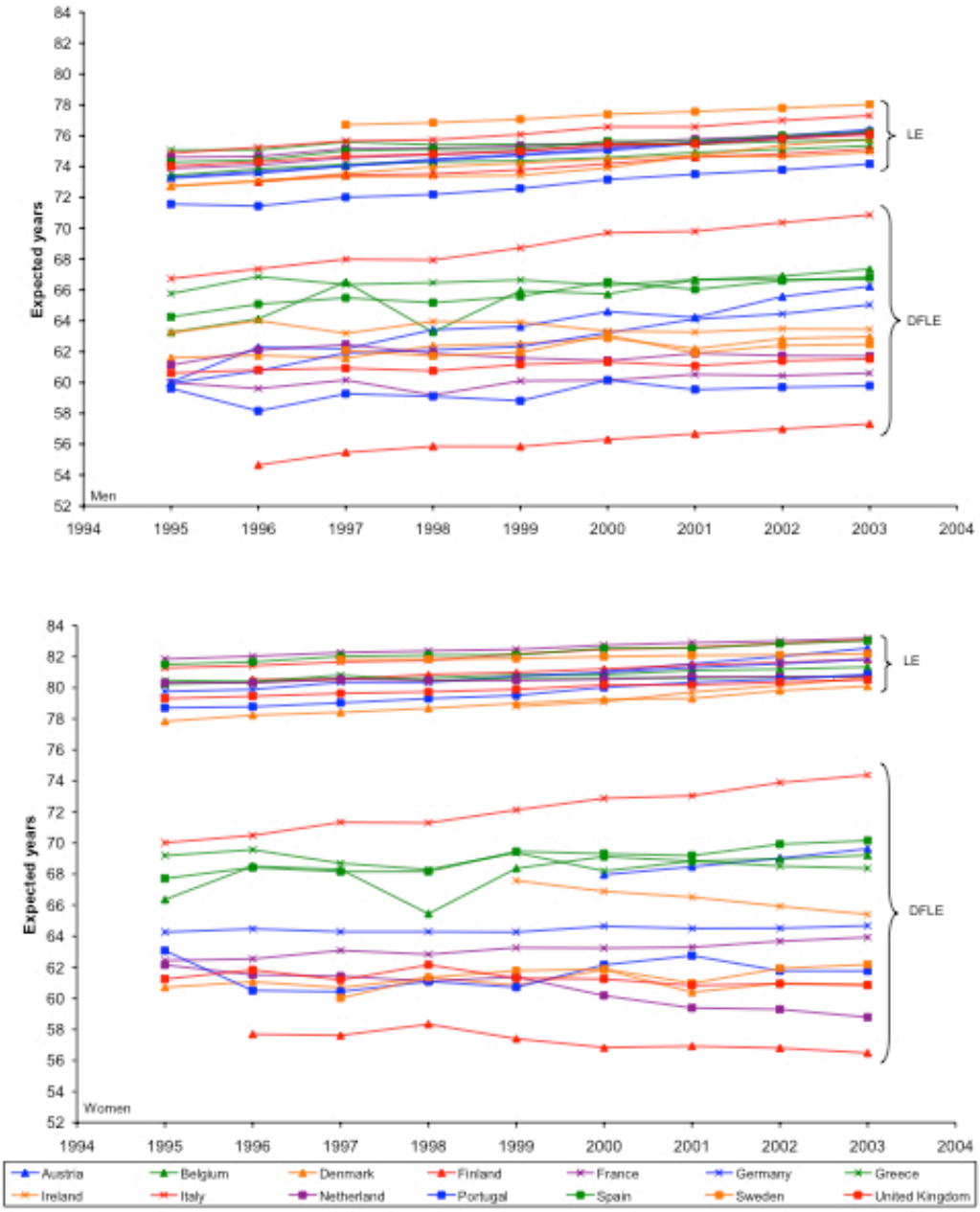


Figure 1.15 - Estimated life expectancy and disability-free life expectancy by gender, in 14 EU member states, 1995-2003. Reproduced with permission from (204).

Encouragingly, the majority of older people in the UK continue to live in their own home. Data from the 2001 Census of England and Wales reveal that 95.5 per cent of people aged 65 years and over, and 79.6 per cent of

people aged 85 years and over, reside in their own home (205).

Nonetheless, it remains clear that an ageing population presents significant health and social care implications. Private expenditure by older people on social care in the UK is projected to rise from £5.9 billion in 2006 to £13.4 billion in 2026 and a parallel shortfall in public funding of social care for older people is projected over this time period (206). Health and social care interventions that halt the development and progression of frailty, and hence prevent disability in older age, would have the potential to improve the general health and well-being of the population. Successful interventions would also provide a clear and powerful opportunity to impact positively on future health and social care expenditure.

1.22 Future research directions

Future translational research to investigate molecular, cellular, tissue and organ frailty will help determine the underlying biological causative mechanisms and, ultimately, aid the unification of diagnosis and treatment. Efforts to unify diagnosis and treatment of frailty should be complemented by a steady evolution of frailty taxonomy models.

Research into epigenetic mechanisms associated with frailty and social vulnerability in early and later life will identify potential targets for future medical and social intervention. Future applied health and social science

research will facilitate the development of complex interventions to halt the development and progression of frailty, and improve the general health and well-being of frail older people.

1.23 Summary

Frailty can be considered to be the result of a complex interaction between genetic, environmental and epigenetic factors. Multiple systems of frailty taxonomy exist but each demonstrates variable utility in prediction of natural history, response to therapeutic intervention and consideration of underlying biological causality mechanisms.

Cumulative ROS mediated nuclear and mitochondrial DNA damage, defective DNA repair mechanisms, telomere shortening and abnormal protein turnover promote cell senescence. These molecular mechanisms are of variable importance in mitotic and post-mitotic cells but the overall effect of cumulative cell senescence is impaired organ physiology. Impairments in brain, endocrine, immune and muscle physiology are considered to be of particular importance in frailty. The complex interaction between the frail brain, frail endocrine system, frail immune system and frail muscles results in a potential vulnerability to adverse outcomes through an inability to maintain homeostasis following physical stress, commonly in the form of an overzealous inflammatory response resulting from infection and physical injury. This prolonged inflammatory response initiates a persistent catabolic state that, although

fundamentally protective in origin, becomes pathological in nature, leading to loss of muscle mass and strength, with attendant decline in functional ability.

Influenced by social vulnerability factors, these adverse outcomes include the 'geriatric giants' of intellectual impairment, instability, immobility and incontinence, along with the associated risks of hospitalisation, admission to long-term care and death. All these adverse outcomes of frailty affect health and wellbeing, and have substantial health and socioeconomic costs. Successful health and social care interventions to halt the development and progression of frailty would have the potential to improve health and well-being in older age, and have substantial health and socioeconomic impact.

Future basic science and translational research will provide greater insight into the underlying causative biological mechanisms of frailty, and identify potential therapeutic targets. Greater understanding of causation will facilitate the unification of diagnosis and treatment. Future applied health and social science research will drive the development of health and social care interventions to halt the development and progression of frailty.

2 Chapter 2. Do home-based exercise interventions improve outcomes for frail older people?

2.1 Introduction

Any attenuation of the prevalence or severity of frailty is likely to have large benefits for the individual, their families and for society. There is accumulating evidence from basic science and applied health research that exercise has the potential to influence the biological mechanisms of frailty and improve associated adverse outcomes through effects on the brain, endocrine system, immune system and skeletal muscle. The role of exercise in the prevention and treatment of frailty will be considered in greater detail and a systematic review to identify whether home-based exercise interventions improve outcomes for frail older people is presented.

2.2 Exercise to prevent and treat frailty

2.2.1 Regulation of DNA damage

Basic science research has begun to identify potential mechanisms of molecular protection through exercise. A 2010 study demonstrated that exercise increases levels of silent information regulators (SIRTs) in

skeletal muscle of ageing rats (207). SIRTs are NAD-dependent protein deacetylases that have been demonstrated to influence DNA damage-repair mechanisms, gene expression and muscle differentiation. An increase in SIRT levels through exercise has the potential to reduce the deleterious effects of biological ageing by moderating the accumulation of DNA damage (207).

2.2.2 Increased neuroprotection

Exercise has also been shown to increase the levels of several other neurotrophic and vascular growth factors, including brain-derived neurotrophic factor (BDNF) and vascular endothelial growth factor (VEGF) (208). Increased neuroprotection through exercise may have the potential to improve the adverse cognitive outcomes that have been associated with frailty.

2.2.3 Increased muscle mass and strength

There is accumulating evidence to indicate that muscle growth is increased through physical activity (PA) in older age, principally through hormonal factors (209). IGF-1 is generated locally in response to physical activity in animal studies, and is believed to have an important role in the development of increased muscle strength and mass through exercise (101, 210). Interestingly, the muscles of frail, nonactive older people appear to retain the capability to respond to IGF-1, suggesting that the

mechanisms triggering muscle growth are likely to remain active during frailty (211). This provides important biological evidence for the potential effects of exercise to improve muscle mass and strength in frail older people.

2.2.4 Reduced inflammation

Recent research has begun to identify potential mechanisms of reduced inflammation through exercise. Regular, moderate exercise increases the release of a number of hormones that exert influence over the immune system, including adrenaline, cortisol and growth hormone (212). Exercise also appears to reduce immune cell expression of Toll-like receptors (TLRs) (213). TLRs are immune cell surface receptors that play an important role in the production of inflammatory cytokines. A long-term reduction in TLR expression may reduce chronic inflammation through a decrease in the inflammatory capacity of leukocytes. A reduction in inflammation through exercise may have particular relevance for the inadequately regulated inflammatory response in frailty.

2.2.5 Improved response to psychosocial stress

Exercise appears to buffer telomere shortening in people who experience chronic stress, potentially via upregulation of telomerase activity. A 2010 prospective cohort study identified an independent association between increased exercise and telomere length in 63 older women (214).

Furthermore, exercise may improve the adverse response to psychosocial stress through effects on the autonomic nervous system and neuroendocrine pathways, including glucocorticoid responses to stress (215)

2.3 Home-based exercise interventions for frail older people

Sarcopenia, one of the key components of frailty, is a potential target for frailty prevention interventions that incorporate exercise to increase muscle mass and strength. Physical activity interventions, particularly those involving strength and balance training, have been successful at improving muscle strength and functional abilities in frail people. Falls prevention and pulmonary rehabilitation interventions, which include exercise components, have previously been demonstrated to be effective at improving important outcomes and are part of routine care (216, 217). A proportion of older people who receive these interventions are likely to be frail, but improved outcomes related specifically to frailty are unclear.

A 2010 systematic review concluded that exercise interventions, particularly those involving strength and balance training, can be successful at improving muscle strength and functional abilities in long-term care residents; a group of older people who are very likely to be frail (218). However, the large majority of older people in the UK live at home

(205). Exercise interventions for older people living at home can be delivered either individually in their homes, or elsewhere as a group activity. A 2005 Cochrane review concluded that both home-based and group-based exercise interventions are associated with improved outcomes for patients receiving cardiac rehabilitation, but that home-based interventions may be associated with improved adherence (219). Furthermore, the 2006 UK Department of Health (DH) white paper 'Our health, our care, our say: a new direction for community services' argued for a different, more community-based approach to people with long term conditions with the provision of more and better quality services summarized as "care closer to home" (220).

A successful home-based exercise intervention for frail older people would have the potential to improve the health and well-being in this vulnerable group at high risk of important adverse health outcomes that have substantial health and socioeconomic costs. To explore the available evidence for frail older people, a systematic review was undertaken on the effectiveness of home-based exercise interventions.

2.4 Methods

2.4.1 Search strategy

A systematic search was undertaken to identify all randomised controlled trials (RCTs) and cluster RCTs that evaluated home-based exercise

interventions for frail older people. A search strategy was developed for Medline, with appropriate amendments for AMED, CINAHL, Cochrane Library, EMBASE, PsychINFO and PedRO, with literature searching to February 2010. A full copy of the search strategy is available in Appendix 1.

2.4.2 Eligibility criteria

The initial search criteria were deliberately broad and all studies that recruited a cohort of older people (defined for this review as a mean age of 70 years or older in the study cohort) were initially considered for inclusion. The individual study description, selection criteria and reported cohort baseline characteristics were then carefully examined by two independent assessors with expertise in both the assessment of frail older people and frailty indices to determine whether the study populations were frail. Studies were considered as frail only if they selected participants or stratified results using an operationalised definition of frailty or if one or more of the five frailty criteria (weight loss, exhaustion, low energy expenditure, slow gait speed or muscle weakness) were identified.

Studies in which the target population were selected on the basis of the presence of a specific medical condition (e.g. chronic obstructive pulmonary disease, heart failure, cognitive impairment, etc), and studies conducted in care home facilities, were excluded.

2.4.3 Types of outcomes

The primary outcomes for this review were measures of mobility (e.g. the Timed Up and Go Test (221)), health-related quality of life indices (e.g. EuroQol Group 5-Dimension Self-Report Questionnaire (EQ5D) (222)) and measures of activities of daily living (ADL, e.g. Barthel index (194)). Secondary outcomes measures were muscle strength, balance, depression, bone strength and adverse outcomes including falls and admission to hospital or long-term care.

2.4.4 Types of interventions

For this review, exercise is defined as an activity requiring physical effort that is intended to improve or maintain fitness. Studies in which the intervention included a mix of home-based and group based exercise were only included if the home-based component formed the greater proportion of the intervention. Entirely group-based exercise interventions were not considered for this review.

The evidence base for falls prevention interventions is already well established and a recent systematic review concluded that the Otago Exercise Programme (OEP), a home-based falls prevention intervention, was effective at reducing falls and mortality (216, 223). However, the evidence base from the falls prevention literature is not necessarily

generalisable to frail older people. Falls prevention interventions are usually targeted at older people who are living independently or with few restrictions in ADL. Strengthening exercises in falls prevention interventions are often of moderate-to-high intensity and are usually performed standing with weights or thera-bands to provide resistance. Balance exercises incorporate dynamic movement and may be of greater risk for frail older people. Additionally the majority of falls prevention interventions include a substantial aerobic component that usually comprises moderate intensity walking/cycling/aerobics for 20-30 minutes, 2-3 days a week. Furthermore, the duration of falls prevention exercise sessions are frequently for between 30 minutes and 90 minutes and this is not necessarily appropriate for frail older people considering the low energy expenditure and fatiguability that characterize frailty. For these reasons, trials in which the intervention had been delivered as the main component of a falls prevention package were also excluded from this systematic review.

2.4.5 Study selection

All titles and abstracts were screened for eligibility by two independent reviewers and any disagreements settled by a third reviewer. Full texts of eligible studies were obtained and reference lists were reviewed for further eligible studies. Two reviewers extracted data using Revman 5.0 software. One reviewer evaluated each study for risk of methodological bias as outlined in the Cochrane Handbook for Systematic Reviews of

Interventions (224). Studies were assessed for allocation sequence generation, allocation concealment, blinding, completeness of outcome data, selective outcome reporting and other potential sources of bias. For each of these domains a judgement of adequate, partially adequate or inadequate was recorded to determine the risk of methodological bias for individual studies. The assessment of bias risk was to inform a sensitivity analysis whereby greatest emphasis was given to the studies that were at lowest risk of methodological bias. Only studies considered to be at low risk of methodological bias would be considered for meta-analysis. If data available precluded meta-analysis then a narrative synthesis was planned.

2.5 Results

The review process is summarized in figure 2.1 using the PRISMA guidelines (225).

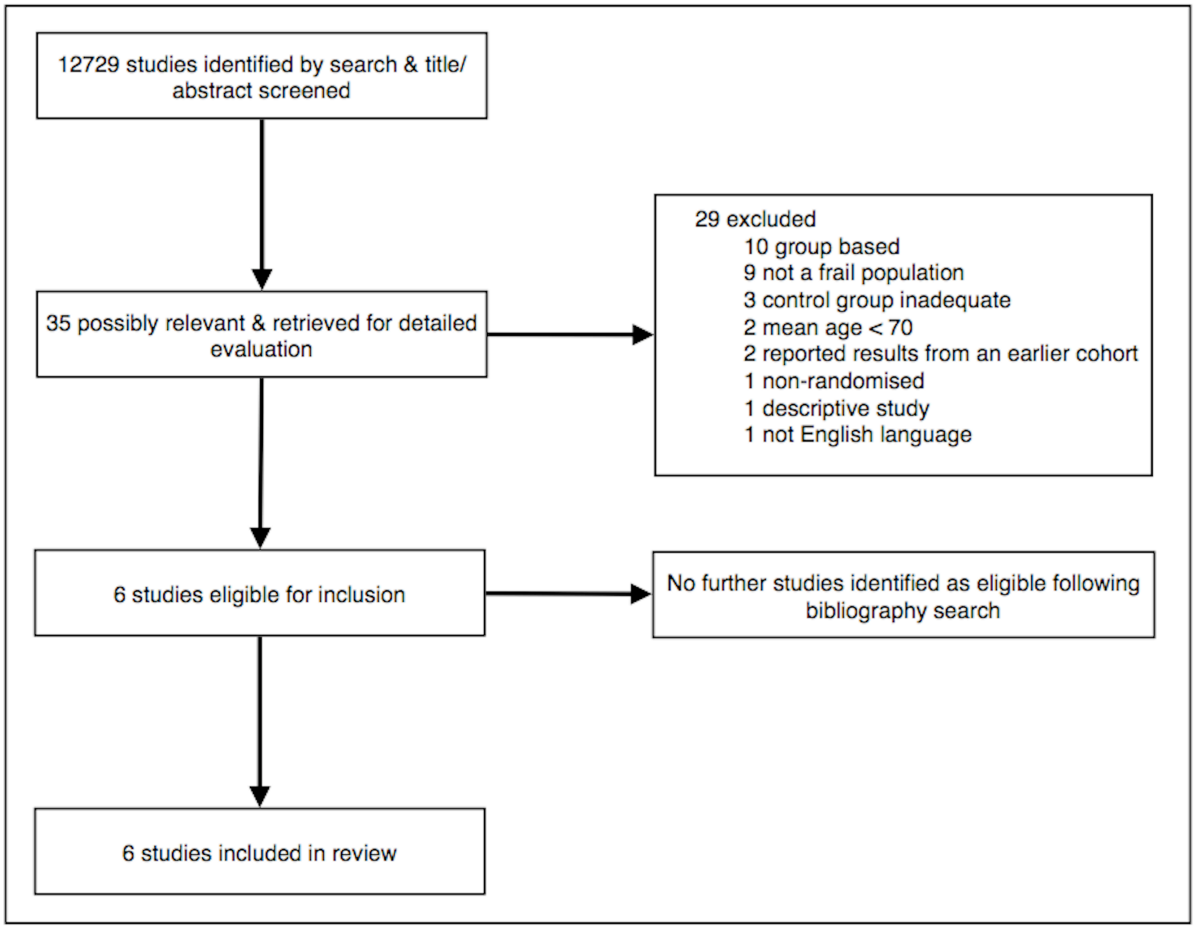


Figure 2.1. PRISMA flow diagram.

2.5.1 Study characteristics

Six RCTs involving 987 participants met the review inclusion criteria (226-231) and are summarised in table 2.1

Study	Year	Country	Sample size	Mean age (SD)	Study participants	Baseline characteristics	Intervention	Delivery	Treatment Frequency/ Duration	Completion (Adherence) rate (%)	Main Findings	Risk of bias
Chandler	1998	USA	100	78 (8)	Aged over 64 years and meeting an operationalised, non-validated definition of frailty - inability to descend the stairs without holding the bannister. Participants then further stratified on the basis of whether they were able to rise from a chair without using their arms	50% male, 50% female 57% were unable to do stairs but able to do chair rise 43% were unable to do either stairs or chair rise	Lower body progressive resistance exercises	Home visits from physiotherapist for each session	3 times per week for 10 weeks	87 (NA)	Strength improved. Greater improvement in more frail group.	High
Gill	2002	USA	188	83 (5)	Aged 75 years and over and meeting an operationalised, non-validated definition of frailty - greater than 10 seconds to perform a rapid gait test or unable to stand from a seated position with arms folded. 'Moderate' frailty if one of two criteria present, 'severe' frailty if both criteria present	20% male, 80% female 47% living alone Mean of 2.1 chronic conditions 62% moderate frailty, 38% severe frailty	Complex, individualized progamme of occupational intervention with progressive resistance, balance and range of motion exercises	Home visits from physiotherapist; average of 16 visits over the 6 month period	Once a day, 3 times per week for 6 months	65 (78)	Improvement in ADL at 6 months. No improvement at 3 months. No improvement in most frail group	Low
Luukinen	2006	Finland	486	88 (3)	Aged 85 years and over with at least one risk factor for ADL disability or history of recurrent falls	21% male, 79% female 31% had severe mobility restriction, 25% had slow walking speed, 20% had severe restriction in ADL score, 19% had poor self-related health Mean of 6.5 (SD 4) medications used	Complex individualised exercise and occupational intervention including a combination of; walking, group exercises, home-based resistance exercises and self care exercises	Unclear	Home-based resistance exercises 3 times a day for 18 months	59 (NA)	Improvement in mobility score. No effect on ADL disability, hospitalisation or long-term care admission.	Low
McMurdo	1995	UK	86	82	Aged 75 years and over, living in sheltered housing with limited mobility requiring the use of a walking aid and ADL dependence requiring home help at least once a week	12% male, 88% female Median Barthel score 19 (range 14-20)	Whole body resistance exercises and range of motion exercises	Exercise cards with diagrams and written explanations. Physiotherapist visit every 3-4 weeks	Once a day for 6 months	73 (NA)	Trend towards improved mobility. No effect on strength, physical condition.	Low

Study	Year	Country	Sample size	Mean age (SD)	Study participants	Baseline characteristics	Intervention	Delivery	Treatment Frequency/ Duration	Completion (Adherence) rate (%)	Main Findings	Risk of bias
Rosie	2007	New Zealand	66	85 (4)	Aged 80 years and over, able to walk 4m with or without a mobility aid, sedentary and mobility-limited. Participants were considered to have a mobility limitation if they were limited 'a lot' in vigorous activity and in one or more activity on the Short-Form 36 Health Survey (SF-36) Physical Functioning Scale (PF-10)	29% male, 71% female 59.1% limited 'a lot' in 5 or more domains of the PF-10 63.6% had no falls in the preceding 12 months	Repeat sit-to-stands using a GrandStand system	One home visit from study researcher followed by one weekly telephone call thereafter	Once a day for 6 weeks	88 (66)	No effect on mobility, ADL or balance	Low
Vestergaard	2007	Denmark	61	81 (3)	Aged 75 years and over in receipt of home care who were housebound but able to get out of a chair and bed	Intervention group took mean of 19.3 seconds (SD 11.6) to complete 5 repetitions of a chair rise, and aerobic exercises control group took mean of 16.4 seconds (SD 5.3)	Flexibility and balance exercises, whole body resistance exercises	Exercise video & booklet. One home visit from exercise instructor followed by bi-weekly telephone calls thereafter	3 times a week for 5 months	83 (89)	Improvement in quality of life. No effect on strength, mobility, physical performance or balance	Moderate

Table 2.1. Summary table of study characteristics, intervention details, main findings and risk of methodological bias.

Key: SD, Standard Deviation; ADL, Activities of Daily Living; NA, not available

The median age was 83 years (range 78 - 88) and the majority of participants were female (median 79% female, range 50 - 88%). Three trials were conducted in Western Europe (228, 229, 231), two in the USA (226, 227) and one in New Zealand (230). A median of 71% (range 8 - 88%) of older people living at home were eligible for trial inclusion and, of those who were eligible, a median of 75% (range 17 - 87%) were recruited. The wide range of values reflects the use of different eligibility criteria and different methods of recruitment in the studies.

Two trials used an operationalised, non-validated frailty model to select and stratify participants (226, 227). Four trials did not use an operationalised frailty model to select participants but reported inclusion criteria or baseline characteristics that identified slow walking speed (228, 229, 231) or physical exhaustion (230) and were therefore considered by consensus to be frail.

All trials assessed participants at the end of the intervention. Median duration of follow-up was six months (range six weeks - 18 months). Two studies included follow-up of 12 months or more (227, 228).

2.5.1.1 Methodological quality & study power

Four trials were assessed as low risk of methodological bias (227-230), one at moderate risk (231) and one at high risk of bias (226). Although the majority of trials were single (assessor) blind, one was unblinded (231). Methods of randomisation were generally well described but an adequate description of the method of allocation concealment was provided in only two studies (229, 230). Only three trials performed an *a priori* power calculation (228-230). Three of the trails recruited less than 100 subjects; only two recruited more than 200 subjects.

2.5.1.2 Exercise interventions, completion & adherence

One intervention included a single component of progressive resistance exercise (226). Two combined progressive resistance exercises with one or more additional components of balance, walking or range of motion exercises (229, 231). Two interventions were complex interventions combining multiple exercise components with an occupational intervention (227, 228). One study used an electronic device that counted the number of sit-to-stands (GrandStand^{TM} system) (230).

Modal treatment frequency was three times per week (range 3 - 21 sessions per week). Modal treatment duration was 6 months (mean 28 weeks, range 6 weeks - 18 months).

Information regarding the percentage of participants who completed the exercise intervention through to follow-up was available in all six studies. Completion rates were generally high (median 83%, range 65 - 88%); interventions of shorter duration generally recorded higher completion rates. Rates of adherence to the exercise intervention, measured as the number of individual exercise sessions undertaken as a proportion of the total possible, were recorded in three studies (227, 230, 231). Various methods were used to define acceptable adherence and rates were generally high (median 78%, range 66 - 89%).

2.5.2 Analysis of primary outcome data

Meta-analysis of primary outcome data from the studies at low risk of methodological bias was precluded by the absence of consistent reporting of data required for calculation and pooling of standardised mean differences (SMDs) for these continuous outcomes. Therefore, a narrative synthesis of the available evidence from all studies is provided that describes the direction and size of effect, its consistency across studies and the overall strength of the evidence. A narrative description of the evidence from the studies at low risk of methodological bias is also provided.

2.5.3 Analysis of secondary outcome data

Meta-analysis of long-term care admission data was possible, using dichotomous data from two trials at low risk of methodological bias (227, 228). These data were pooled for meta-analysis using random effects modeling (Revman 5.0 software) and are presented as risk ratios in a forest plot (figure 2.2). It was not possible to pool continuous outcome data for the other secondary outcomes due to the data limitations described above and a narrative synthesis is presented.

2.5.4 Primary outcomes

2.5.4.1 Effects on mobility

Four trials reported an outcome measure relating to mobility, using various measures of gait speed (228-231). Improved gait speed was reported in one trial (228), a trend towards improved gait speed was reported in one further trial (229) and gait speed did not improve in two (230, 231).

2.5.4.2 Effects of health-related quality of life

One trial reported an improvement in quality of life, measured using the EQ5D (231). The other trials did not record quality of life measurements.

2.5.4.3 Effects on activities of daily living

Measures of Activities of Daily Living (ADL) were reported in four trials (227-230). Improvements in ADL were reported in one trial (227), no improvements in ADL were reported in the other three trials (228-230).

2.5.5 Secondary outcomes

The meta-analysis of long-term care admission data is presented in figure 2.2. A non-significant trend towards reduced long-term care admission is observed (pooled risk ratio 0.89, 95% confidence interval 0.55-1.45).

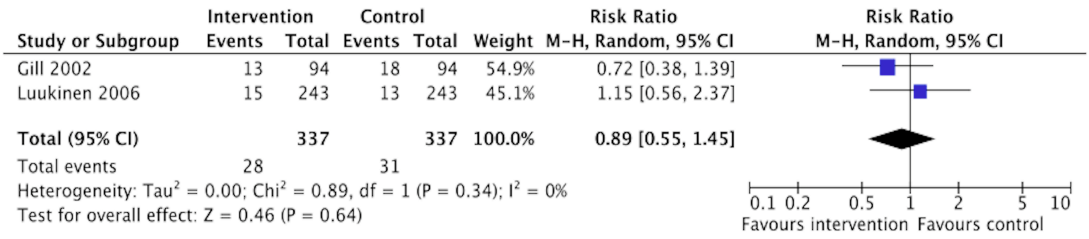


Figure 2.2. Forest plot presenting individual and pooled risk of long-term care admission from two trials at low risk of methodological bias.

Three trials measured muscle strength using upper and lower body strength (226, 231) or grip strength (229). One trial reported improved lower body strength (226). There was no improvement in either upper or lower body strength in one trial (231). No improvement in grip strength was recorded in the one trial that measured this outcome (229). No

improvement in general physical performance was reported in one trial (231).

Improved balance was reported in one trial (228) but there was no effect on balance in three trials (229-231). There was no effect on depression (228), bone density or flexibility (229). Hospitalisation rates were not reported in any trials.

2.5.6 Adverse outcomes

Between group differences in adverse outcomes were reported in only two trials (227, 228). Increased angina diagnoses were recorded in one trial (227) but no differences in fractures, musculoskeletal pain or death were reported (227, 228).

2.5.7 Trials at low risk of methodological bias

There were four high quality trials at low risk of methodological bias (227-230). One trial selected and stratified participants using an operationalised, but non-validated, measure of frailty (227). Participants were considered for inclusion and defined as being frail if they took >10 seconds to walk three metres, or if they were unable to stand from seated with both arms folded. Participants with one of the two criteria were defined as moderately frail; participants with both criteria were defined as severely frail. This relatively large trial (n=188) investigated the effects of a six month complex individualised exercise and occupational

intervention and reported an improvement in disability score at seven months for people with moderate frailty (227). This improvement was maintained at 12 months follow-up. There was no effect for people with severe frailty.

Although the other three trials at low risk of methodological bias recruited frail older people they did not use an operationalised measure of frailty to stratify results. One large trial (n=486) that investigated a complex individualized exercise intervention reported improved mobility and balance but no effect on ADL (228). One smaller trial (n=86) of a six month intervention in a cohort living in sheltered housing reported a trend towards improved mobility but no effect on ADL, grip strength or balance (229). One small trial (n=66) of a six week intervention reported no effects on mobility, ADL, grip strength or balance (230).

None of the four high quality trials reported overall effects on the quality of life of participants.

2.6 Discussion

This systematic review summarizes the evidence from research trials that recruited 987 participants. Strengths of the review include a robust search strategy and rigorous review procedures that included a detailed assessment of risk of methodological bias using well recognised methods. A potential weakness of the review is that, although a

consensus decision was reached regarding whether individual trials included frail older people on the basis of the frailty phenotype, only one high quality trial both selected participants and stratified results using an operationalized measure of frailty.

Included trials were generally of high methodological quality. However, individual sample sizes were frequently small and *a priori* power calculations were not routinely completed, giving rise to the possibility of Type II statistical error due to small sample size. Limitations of data analysis and reporting precluded meta-analysis of primary outcome data, which could otherwise have pooled statistical power. Guidelines for developing RCTs aimed at preventing functional decline and disability in frail older people are available (232) and reference to these guidelines will help in the development of future RCTs. Standardisation of outcome measures and reporting will further aid the future synthesis of evidence for meta-analysis.

One high quality trial used an operationalised, non-validated measure of frailty to both select and stratify participants. This trial reported an improved disability score in people with moderate frailty and this was maintained at 12 months. No improvement was reported for people with severe frailty. Other higher quality trials reported inconsistent effects on mobility and disability. None of the four high quality trials reported effects on quality of life.

Meta-analysis of data from two trials at low risk of methodological bias demonstrated a non-significant trend towards reduced long-term care admission. The relatively low rates of long-term care admission in these two trials and wide confidence intervals identify a requirement for future long-term trials that are adequately powered to detect a significant difference in this important outcome.

Generally high rates of completion and exercise adherence suggest that home-based exercise interventions are acceptable and feasible for frail older people. This supports the similar finding from the earlier systematic review of exercise interventions for older people living in care homes which also identified high rates of intervention completion and adherence (218).

2.7 Conclusion

There is preliminary evidence from one high quality trial that selected and stratified participants using an operationalised measure of frailty to suggest that home-based exercise interventions may be effective at improving disability in community-dwelling older people with moderate, but not severe, frailty. Operationalised measures of frailty were not used to stratify participants in the other high quality trials and inconsistent effects of exercise interventions on outcomes including mobility and disability were reported. There is significant uncertainty regarding the

effects of home-based exercise interventions on important outcomes including quality of life and long-term care admission for the frail elderly.

Home-based exercises are a potentially simple, safe and widely applicable intervention to prevent dependency decline for frail older people. Adequately powered RCTs that use validated measures to select and stratify frail older people, and that incorporate long-term follow-up of important outcome measures including mobility, disability, quality of life and long-term care admission, will help address the uncertainties that have been identified in this review.

3 Chapter 3. Development of the Home-Based Older People's Exercise (HOPE) programme

3.1 Introduction

A home-based exercise intervention for frail older people is an example of a complex health intervention. The Medical Research Council (MRC) framework for the development and evaluation of complex health interventions identifies the key elements of the design and evaluation process (233). The MRC framework has therefore been adopted to develop and evaluate the Home-Based Older People's Exercise (HOPE) programme, an exercise programme to improve the mobility and daily living activities of frail older people living at home. This chapter describes the development of the HOPE programme with reference to the MRC framework.

3.2 Development of the HOPE programme

The HOPE programme has been developed by synthesising information from four key domains: a systematic literature review to identify the evidence base for home-based exercise interventions for frail older people (Chapter 2); a process of intervention modelling work

incorporating a series of multiperspective focus group meetings, an information provision needs assessment exercise and a Delphi consensus approach; a review of the relevant behaviour change literature and a review of international consensus guidelines on the development of exercise interventions for older people. This process is illustrated schematically in figure 3.1 and an initial brief description of the four key domains is provided in 3.2.1 - 3.2.4.

Following the initial brief description, this chapter (Chapter 3) focuses on the intervention modelling work, consensus process and behaviour change literature and is presented in four sections. Section 1 (3.3 - 3.9) discusses the series of multiperspective focus group meetings; section 2 (3.10 - 3.14) presents the information provision needs assessment exercise; section 3 (3.15 - 3.19) presents the Delphi consensus process and section 4 (3.20 - 3.22) discusses the relevant behaviour change literature. The following chapter (Chapter 4) describes how the information obtained through the development process was synthesised into the HOPE programme and includes a complete description of the intervention.

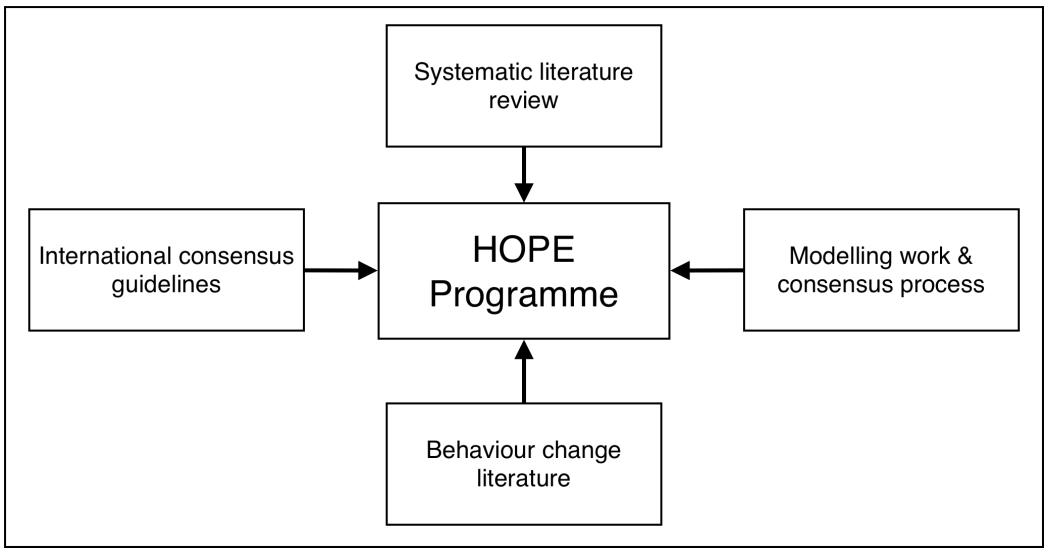


Figure 3.1. Schematic representation of the development of the HOPE programme by synthesising information from four key domains.

3.2.1 Systematic literature review

The systematic review of the literature (Chapter 2) was conducted to identify RCTs of high methodological quality that investigated home-based exercise interventions for frail older people. This review was complimented by an earlier systematic review of exercise interventions for frail older people in long-term care (218). The key components of the exercise interventions in the RCTs of high methodological quality were used to inform the frequency, intensity and duration of the intervention.

3.2.2 Modelling work and consensus process

Briefly, a series of multiperspective focus group meetings with frail older people and experienced healthcare professionals were conducted to

model the HOPE programme. Views were first sought from frail older people living at home who had recently received therapy-based interventions at Westbourne Green Community Hospital, a residential NHS intermediate care site in Bradford. The multiperspective focus group meetings with frail older people incorporated an information provision needs assessment exercise to inform the design of the HOPE manual. Views were also sought from experienced healthcare professionals to facilitate the development of the HOPE programme by gaining valuable insights.

Following the series of focus group meetings a Delphi consensus process (234) was conducted to seek agreement on the key principles to be incorporated into the HOPE programme.

3.2.3 Behaviour change literature

It is recognised that people can contribute to their overall health and well-being by adopting or avoiding certain health behaviours (235). Choice of health behaviour is influenced by multiple factors, including personality, cognitive and socioeconomic factors. To facilitate health behaviour change, a series of theoretical frameworks have been developed that consider these important factors (235). These theoretical frameworks were reviewed to incorporate appropriate behaviour change techniques into the HOPE programme and are considered in greater detail in 3.20 - 3.22.

3.2.4 International consensus guidelines

International consensus guidelines on the development of exercise interventions for older people from the American College of Sports Medicine (ACSM) and the American Heart Association (AHA) were reviewed (236). These guidelines recommend that exercise interventions for older people should be multi-dimensional and include exercises to improve whole body muscle strength, mobility, balance and aerobic capacity.

3.3 Section 1: Modelling of the HOPE programme

3.4 Background

The MRC framework for developing and evaluating complex interventions has identified that intervention modelling is a critical phase of development during which it is advantageous to involve service users in a co-design process (233). Focus groups are considered to be a particularly useful method of exploring people's knowledge and experiences; the group process is considered to help participants explore and clarify their views (237). Multiperspective interviews with patients, families and professionals can provide insight into individual needs and facilitate the integration of suggestions for developing services (238). A series of multiperspective focus group meetings with frail older people and healthcare professionals were therefore conducted to develop greater understanding about the nature and scope of a home-based exercise intervention for frail older people. Practical difficulties and time constraints precluded involving families in the series of focus group meetings.

3.5 Methodology

Views were sought from frail older people living at home who had recently received therapy-based interventions, to learn from their experiences and

consider coping strategies to draw on these for motivational purposes. Intermediate care facilities provide a range of therapy-based services to frail older people to promote recovery from illness, prevent unnecessary hospital admission, support discharge and maximise independent living (239). Two focus group meetings were therefore chosen to take place at Westbourne Green Community Hospital, a residential NHS intermediate care site in Bradford where therapy-based rehabilitation typically follows an acute illness prior to return home. The meetings were semi-structured interviews with a small number (3-5) of older people who were considered to be frail by the nursing and therapy staff. The semi-structured interview schedules were informed by a series of key questions that are presented in figure 3.1. The meetings were audio-recorded and contemporaneous field notes were taken. Written, informed consent was taken from all participants. Full ethics approval was given by Bradford Research Ethics Committee (REC reference 09/H1302/55).

Focus Groups 1 & 2

1) What factors contribute to daily functional limitations for frail older people living at home?

2) How is the concept of exercise in old age understood by frail older people?

3) What are frail older people's perceived barriers to involvement in a targeted exercise programme?

4) What would motivate frail older people living at home to complete a targeted exercise programme lasting 12 weeks?

Figure 3.1. Key questions that informed the semi-structured interview schedules for focus group meetings 1 & 2.

3.5.1 Sampling frame

As residence in intermediate care is for a relatively short period of time, convenience sampling methods were used to select participants for the focus group meetings. Although convenience sampling was used, purposive sampling methods were also employed to guide individual participant selection. This ensured that both sexes were represented in the sample and that the sample included frail older people with a range of living circumstances in different types of housing. To gain insight into perceived barriers to successful exercise participation, frail older people who expressed difficulties in engaging with rehabilitation in intermediate care were sought alongside those who engaged with greater ease.

Experienced community based healthcare professionals were invited to a third focus group meeting at the Bradford Institute for Heath Research. The views of community physiotherapists, who have considerable experience in providing therapy services to frail older people in the community, and community matrons, who are experienced nurses with advanced practitioner skills working with frail older people, were also sought to facilitate the development of the HOPE programme. The meeting schedule for healthcare professionals was informed by key questions that are presented in figure 3.2.

Focus group 3

1) What limitations in the functional ability of frail older people living at home are commonly seen by community physiotherapists?

2) What types of exercises are likely to be effective at improving functional abilities of frail older people living at home?

3) What would motivate/aid frail older people to adhere to a home-based exercise training programme?

4) What are potential barriers to exercising in the home for frail older people?

Figure 3.2. Key questions that informed the semi-structured interview schedules for focus group meeting 3.

The phenotype model of frailty (3), and the associated adverse health consequences, were introduced to participants in a short presentation at the beginning of the meeting to stimulate initial discussion. The meeting was audio-recorded and contemporaneous field notes were taken. Written, informed consent was taken from all participants.

3.5.2 Data analysis

The data analysis was conducted by myself, with expert guidance from Mary Godfrey, reader in Health and Social Care, Academic Unit of Elderly Care & Rehabilitation, University of Leeds.

Interview transcripts and field notes were analysed using grounded theory methods (240). Following initial data familiarisation, key emerging issues, concepts and themes were identified and coded to aid data interpretation. All generated data were analysed alongside new data collection using constant comparison methods (241) to allow refinement of research questions and identification of new avenues of inquiry throughout the research process. Data from the meetings with frail older people and healthcare professionals were initially analysed separately and emerging themes were compared to identify areas of commonality or disagreement.

3.6 Results

A total of nine participants took part in the two focus group meetings with frail older people. The median age of the nine participants was 87 years (range 80 - 97 years). Five participants were female and four were male. A range of living circumstances were represented; four participants lived alone, three lived with a spouse, one lived with her daughter and one lived with a friend. Different home dwellings were identified including houses with/without stairlifts and bungalow accommodation.

Seven experienced healthcare professionals (one head of therapy services, one physiotherapy clinical coordinator for older people, three community physiotherapists and two community matrons) took part in the meeting with healthcare professionals. The results from the focus group meetings with frail older people and healthcare professionals are

presented separately. Two case studies are presented to help illustrate the challenges experienced by frail older people living at home.

3.6.1 Frail older people

3.6.1.1 Wanting to keep on going

The overarching theme identified from the focus group meetings with frail older people was 'wanting to keep on going'. Participants identified a range of constraints that prevent frail older people from keeping going, including physical and environmental constraints and examples of these are presented below. A range of coping strategies and mechanisms to overcome these constraints were discussed by participants. It became clear that some constraints were more surmountable than others, and the social support network of family and friends was identified as a particularly important modifying factor.

3.6.1.2 Trying to cope with physical constraints

Frail older participants identified that muscle weakness, joint pain/stiffness and physical fatigue are important physical constraints that can make keeping going more difficult. A particular constraint was muscle weakness in the important muscle groups that are required to complete the basic mobility task of standing from a chair. Illustrative comments describing important physical constraints experienced by frail older people are provided below.

"That's what it is with me, it's legs, it's legs with me, that's why I had to go to live with my daughter because I couldn't manage my own house at the finish, it was getting too much for me with having my own house. Cleaning the house, washing and that, it got too much for me because I couldn't move about when my legs were really bad, so I had to keep going in hospital and coming out." (Participant 2, focus group 1. 90 year old lady living with her daughter in a house with stairs)

"Yes, that's what does me, pushing up from a chair." (Participant 2, focus group 2. 89 year old gentleman living with his wife and daughter in a house with a stairlift)

"(Getting up out of a chair is) one of the hardest parts, yes." (Participant 3, focus group 2. 80 year old gentleman who lives with his wife in a semi-detached house with stairs)

"It's the same in the morning when I get off of bed, I've got to stand for nearly five minutes before I've got my balance enough to move my legs." (Participant 2, focus group 2. 89 year old gentleman living with his wife and daughter in a house with a stairlift)

"I think really, the outstanding fact I think comes in front of steps, and that is the pain factor." (Participant 1, focus group 1. 86 year old gentleman, widowed two years previously, living alone in a bungalow).

"Yeah, well I just used to go… my daughter used to take me shopping a bit, that's about all we did, and I used to go out for my tea one day. I didn't do a lot because I didn't have much energy." (Participant 3, focus group 1. 87 year old lady living alone in a bungalow).

3.6.1.3 Trying to cope with environmental constraints

Stairs were identified as an important environmental constraint that present a significant challenge to frail older people. Struggling with stairs inside the home can make it difficult for older people to manage activities of daily living. Struggling with stairs to the front door and stairs at the homes of family and friends restrict frail older people to the immediate home environment and can limit both social participation and social support networks. However, coping strategies employed by frail older people can make it easier to overcome the challenges posed by environmental constraints.

"I find (steps) difficult, really difficult. It's okay if you haven't got your steps, but if you have, you've got to struggle with them. I (live

at) my daughter's and I have to go upstairs to the toilet and I struggle going up you see, I manage to only go once usually, because I can't manage any more. They're very steep, her steps." (Participant 2, focus group 1. 90 year old female living with her daughter in a house with stairs)

"I thinks steps are difficult for everybody, I would say that, would you?" (Participant 5, focus group 1. 87 year old lady who lives with a friend in a house with a stair lift).

3.6.1.4 Managing to cope despite physical and environmental constraints

Although a range of physical and environmental constraints were identified, it became clear that older people in the two focus groups had the capability to overcome these potential constraints. Personal determination to keep going appeared to help overcome many of the physical constraints. Environmental constraints could frequently be overcome through environmental modification, such as grab-rails and stairlifts that make it easier to keep going. Methods to make it easier to cope with environmental constraints based on practical experience were identified by frail older people, such as raising the level of the bed to make it easier to get out of bed in the morning. Furthermore, the home environment itself could be used to make it easier, for example by using furniture for support when walking.

"So we bought two reclining chairs and they lift you forward and lift you at the same time." (Participant 2, focus group 2. 89 year old gentleman living with his wife and daughter in a house)

"It's four steps going from the road outside and a handrail at each side. And inside we've got the bedroom steps that are just inside the front door, there's a chairlift, a walk-in shower - sit-down." (Participant 4, focus group 1. 83 year old gentleman who lives with his wife and grandson in a house.)

"Well, it's a terrace house, the front door is only one step and there is rails that have been put up both sides, so you can pull yourself up with that one step. And inside, we've got a chairlift." (Participant 5, focus group 1. 87 year old lady who lives with a friend in a house)

"Now they've stopped me going home three times, the welfare people...first they grade my bed is too low...and they can't fathom out how to raise our bed five inches. So if they can't do it in the end, I'm going to scrap the bed - it's a new bed - and we'll buy two single beds. And if they've got wooden legs, within an hour, I'll have legs made for it and everything." (Participant 2, focus group

2. 89 year old gentleman living with his wife and daughter in a house with a stairlift)

"Well you try to arrange… well, we do, try to arrange the house so that when you're walking round...there's a settee that you can hold onto and the chair and then by that time, you get into the kitchen. When you get to the kitchen, you've got your units and then we have a trolley what we put our meals on and push it in. And you work round which you think is best for yourself and easy and easiest for yourself." (Participant 5, focus group 1. 87 year old lady who lives with a friend in a house.)

3.6.1.5 Managing to cope through the help of family and friends

The social support networks of family and friends were identified as being particularly important in helping frail older people to cope and manage to keep going. Social support networks were important both for people living alone and people living with family and friends. Illustrative comments are provided below.

"I've got a good daughter twenty minute away in Guiseley...so if I need anything, I've got all I need." (Participant 1, focus group 1. 86 year old gentleman, widowed two years previously, living alone in a bungalow)

"But I would be able to manage at home because my daughter comes you see, comes most days and sees to me." (Participant 3, focus group 1. 87 year old lady living alone in a bungalow)

"Yeah, well I just used to go… my daughter used to take me shopping a bit, that's about all we did, and I used to go out for my tea one day." (Participant 3, focus group 1. 87 year old lady living alone in a bungalow)

"I'm lucky, I've got the wife and grandson to look after me, I'm getting a carer coming in to wash and dress me in the mornings, so that'll make it a bit better." (Participant 4, focus group 1. 83 year old gentleman living with his wife and grandson in a house with a stairlift)

"We're lucky because we've got a fairly big family, there's always somebody pops in to see we're alright and do things for us, so we're lucky that way." (Participant 4, focus group 1. 83 year old gentleman living with his wife and grandson in a house with a stairlift)

3.6.2 Healthcare professionals

3.6.2.1 Managing to keep moving

The overarching theme identified from the focus group meeting with healthcare professionals was that frail older people need to manage to keep moving in order to remain independent. Healthcare professionals talked more about individual movements that they considered crucial to remaining independent when compared to frail older people. A particularly crucial movement was considered to be the sit-to-stand, as this enables frail older people to undertake basic needs, such as going from the bed or chair to the toilet. Climbing the stairs was considered to be another crucial movement to enable frail older people to remain independent at home.

A further important theme identified by healthcare professionals was that, although exercise has the potential to help frail older people keep going, there are a range of personal and health constraints that are important potential barriers to successful exercise participation. Furthermore, it was identified that frail older people may be constrained by a fear of falling and associated loss of confidence, which can overwhelm even those with the physical abilities to keep going.

3.6.2.2 Personal constraints

Limited personal life experience with exercise was considered to be an important potential barrier to successful participation. Similarly, it was

considered that cultural expectations could influence the uptake of exercise interventions by frail older people. Explaining that exercise interventions can potentially help frail older people to do simple, yet crucial tasks and giving a purpose to the exercises to make them more meaningful were considered to be particularly important methods of increasing motivation and participation.

> "And a lot depends on their life up to that point as well, doesn't it, if they've never exercised in their life up to that point, it's not been part of their daily routine, to suddenly be faced with this person telling them they've now got to exercise, it's a huge cultural shock, isn't it? And they can't understand why it's going to make any difference now at this point in their life." (Community physiotherapist 3)

> "Yeah, you said about explaining to people, it's like this exercise might seem pointless, bridging is one I can think of, lying on a bed and lifting your bottom off the bed, people say 'It's a strange exercise, I'd never need to do that' yeah, but that's the same muscles that are going to lift you out of the chair, it's the muscles in your backside. And once you've explained that to them, as long as they can understand that 'oh yeah, I can see that' and then they relate to it and will practice it." (Physiotherapy clinical coordinator for older people)

"I've also found from my experience, that if you take the time at the beginning to explain why the exercise is actually going to help them...in ways that they understand, they can actually start to think 'well actually, I need to do this' rather than 'I'm just doing this because this medical person has told me I have to do it'." (Community physiotherapist 3)

"Once they get used to doing that then if they move on to getting out of a chair they'll really feel they've achieved something. They know they're starting with this because it's a way of building their muscle so they'll be able to get out of a chair. When they do move on to getting out of a chair they'll really feel they've actually achieved something." (Community Matron 2)

3.6.2.3 Health constraints

Important health constraints were identified, including pain, low mood and cognitive impairment. Day-to-day variability in these health constraints means that frail older people often report having 'good days' and 'bad days', which can influence their motivation to participate in exercise.

"One thing we've not mentioned is pain and pain is a big barrier to exercise and particularly with this group of people and they're frightened to exercise because it hurts when they're beginning to

move and a big part of our education is actually if you move more frequently, you might experience less pain. That's quite a difficult thing to accept really." (Physiotherapy clinical coordinator for older people)

"I've just thought that a big barrier for my particular group of patients, is their mood, if they're depressed, they're less likely to engage with anything." (Community Matron 1)

"But it's how they feel they're doing themselves, if they're not feeling very well, they lack the motivation because they can't be bothered for that day and you hear older people say they've had a good day or a bad day." (Community Matron 2)

"What I've found is there's a huge variability in that somebody one day will be really good and really seem to be progressing and then you'll go the next week and they'll be 'I really have had a bad week, I'm not so good'. You obviously need to catch them on a good day to get anywhere and they have a lot of bad days and it's almost one step forward, two steps back sometimes and that can be quite difficult." (Community physiotherapist 1)

"Or they'll even contact us and cancel and say "I'm not well" and don't want us to call and then to try to get back in there, if you

phone, they say “oh, I’m still not well” and then that’s it, they just don’t want you to come anymore sometimes." (Community physiotherapist 2)

3.6.2.4 Constrained by fear of falling

Being constrained by fear of falling and loss of confidence, particularly following a recent medical illness, were identified by healthcare professionals as important factors influencing the ability to keep going. These were considered to be particularly important because even if frail older people have the physical capability to manage the simple movements to keep going, a fear of falling and associated lack of confidence can be overwhelmingly constraining.

"One of the big issues as well is confidence issues, if they have just come out of hospital and returned home, they tend to just want to sit in their favourite chair and any movement from there, it fills them with fear sometimes. So they don’t want to move because they don't feel safe to move, so that’s another issue sometimes." (Community physiotherapist 4).

"I think (confidence) is probably the biggest thing, a lot of patients we see and we’ve worked with, we might think they have the physical capability to do something but if they haven’t got the confidence, it doesn’t actually make a difference at the end of the

day. And a lot of that confidence is around them having their postural stability to be able to do something and not be frightened that they're going to fall over or they're frightened to let go of the support of the walking aid or the back of the chair to do things; functional activities." (Physiotherapy clinical coordinator for older people)

3.6.3 Case studies

A case study is a detailed examination of a single example (242). Description and explanation of individual cases are part of the steps towards generalisation and the closeness of case studies to real-life situations is considered to facilitate the development of a richer understanding of reality (243, 244). Two case studies are therefore provided to illustrate the real-life constraints that are experienced by frail older people who want to keep going (figures 3.2 and 3.3).

Case study 1

LL, a 90 year old lady who was widowed many years earlier. She lives with her daughter in a three bedroom semi-detached house with stairs and is usually mobile with a walking stick. The district nurses attend twice a week to dress her leg ulcers.

After the death of her husband at the age of 52 she lived alone for many years but, being a very house-proud lady, eventually found that it got too much to clean the house due to increasing weakness in her legs and pain in her feet. She felt that the house was getting neglected and, following a number of hospital admissions, has recently decided to move in with her daughter, where she is now very happy. She currently spends much of the day in her upstairs bedroom but tries to come downstairs to have a meal with her daughter. When she is downstairs, she occasionally walks around with her stick and holds on to the furniture a bit for support.

She finds the stairs especially difficult. She struggles up the stairs, which are very steep, and usually only manages this once a day. The toilet is upstairs, so if she comes down for a meal she has to go back up again for the toilet. She maintains a spirit of determination and perseverance, which she feels she gained during the war, when she had to look after herself and her daughter while her husband was away.

Figure 3.2. Case study 1.

Case study 2

SH, an 89 year old gentleman who lives with his wife in a house with stairs. He is usually mobile at home with a Zimmer frame and his house has a number of aids and adaptations that both he and his wife use, including a wheelchair, two recliner chairs, grab rails, a stairlift and a bath winch. He had to buy some of these himself and has been frustrated by the amount of time that it has taken social services to provide and fit the aids and adaptations.

He finds it very difficult to get up out of a chair, due to generalised weakness in both arms and legs. He also finds it particularly difficult to get up out of bed in the morning and needs around 10 minutes to do this. He has had a number of recent trip falls, which have resulted in rib injury and, more recently, a hip fracture.

His wife has been wheelchair-bound for the last 18 months and has required increasing amounts of care from himself and his daughter. He feels that his daughter does a great deal for both himself and his wife and he is worried that he will have to rely on his daughter more following his recent hip fracture. His daughter has a job of her own but comes over early every morning to get his wife out of bed and make the breakfast. She also comes over every night, regularly takes his wife to the doctor for appointments and does all of their washing and shopping.

Figure 3.3. Case study 2.

3.6.4 Triangulation of data by exploration of the research literature

A 2009 UK Department of Work and Pensions report (245) presented the results from five UK national surveys: the British Household Panel Survey (BHPS); English Longitudinal Survey of Ageing (ELSA); Family Resources Survey (FRS); General Household Survey (GHS) and Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). The four surveys recorded disability in a total of 45,340 older people

using a variety of instruments that measure different domains of instrumental activities of daily living.

The results from the five surveys indicate that difficulty with stairs is particularly common in older people, with a median prevalence of 26.3% (range 20.7-27.4%). Difficulty getting in and out of bed is less common, with a median prevalence of 8.6% (range 7.3-9.8%). Other areas of difficulty in instrumental activities of daily living are shopping (median prevalence 25.5%, range 12.2-38.7%), bathing (median prevalence 16.7%, range 14.1-16.9%) and, less commonly, toileting (median prevalence 4.5%, range 4.4-4.6%).

Interestingly, although these results from national surveys support a proportion of the key findings from the focus group meetings, one key theme emerging from the focus group meetings with frail older people and healthcare professionals is not reported in the surveys. Both frail older people and healthcare professionals identified difficulty in standing up from a chair as a key limitation that adversely affects the ability to keep going. However, standing from a chair is not included in any of the activity of daily living instruments that were used to gather data for the five national UK surveys.

3.7 Reflexive account

A vibrant discussion throughout the series of multiperspective focus group meetings has provided a rich dataset giving deep insight into the experiences and constraints of frail older people who are trying to keep going. The focus group meetings have provided an opportunity to learn from the rich narrative presented by frail older people and healthcare professionals. Although it is possible that the meetings may have been influenced by the thoughts of the main facilitator (AC) it was notable that the majority of discussion during the focus group meetings was undertaken by frail older people and healthcare professionals, with a relatively low requirement for facilitator steering and prompting.

An important theme emerging from the focus group meetings was that frail older people can be constrained by difficulty in standing up from a chair. Standing up from a chair is a critical movement that is necessary for older people to ambulate around the home and get up and go to the toilet. Reduced ability to stand up from a chair has been associated with increased risk of disability and falls (246). This constraint would not have been identified by a review of national survey data alone as standing up from a chair is not included in any of the instrumental activity of daily living measures that have been used in five UK national surveys.

In addition, it is difficult to get an impression of the weighted importance of IADLs from surveys and a greater sense of the importance of IADL

difficulties can be gained from the rich narrative that has been provided in this series of multiperspective focus group meetings with frail older people and healthcare professionals.

3.8 Discussion

It is clear that the frail older people in our focus group meetings want to keep going and will often struggle through difficult circumstances to remain living independently at home. Both frail older people and healthcare professionals identified that loss of muscle strength in the legs and arms can make keeping going more difficult. This loss of muscle strength makes it harder for frail older people to manage to keep doing the important basic mobility tasks of standing from a chair, climbing stairs and getting out of bed in the morning.

Loss of muscle strength can be compounded by other constraints including pain, fatigue and acute exacerbations of chronic medical conditions. However, frail older people are able to keep going and overcome many of these often considerable physical constraints. These physical and health constraints are potential barriers to successful participation in exercise interventions and participants emphasised the importance of considering these constraints when developing exercise interventions for frail older people. Some constraints appear to be more difficult to overcome than others; physical fatigue and fear of falling are

particularly problematic for a frail older person who is struggling to keep going.

Environmental constraints were also identified as making it more difficult to keep going. However, these environmental constraints appear to be more easily overcome than some physical and health constraints through the use of simple aids and adaptations. The importance of support from family and friends was highlighted and, where possible, the involvement of family and friends is likely to be important for the successful engagement of frail older people in exercise interventions.

3.9 Conclusions

A home-based exercise intervention for frail older people should consider including exercises to improve leg and arm muscle strength to help with the important movements of standing from a chair, getting out of bed and climbing stairs. To help engage frail older people, the functional purpose of each exercise should be explained clearly to participants.
Consideration should be given to potential barriers to participation, particularly fatigue, fear of falling and joint pain/stiffness. Furthermore, the likelihood of frail older people having good days and bad days, which may impact on intervention adherence, should be considered. Some barriers to participation, such as loss of confidence and physical fatigue, are likely to be more constraining than others and factors to accommodate this should be incorporated into the intervention. Family and friends are a

powerful potential modifying factor and, if practical, their involvement in the intervention should be sought wherever possible.

3.10 Section 2. Information provision needs assessment

3.11 Background

Visual impairment in older age has been described as a 'hidden' disability and a significant unmet need for provision of information to visually impaired older people has been identified (247). Visual impairment is common in older people, especially older women, and the prevalence increases from 6% in those aged 75-79 years to 37% in those aged 90 and older (248). Around half of visually impaired older people have a mild impairment, the other half have a moderate to severe impairment (249). An independent association between frailty and visual impairment has previously been reported (250).

The United Kingdom (UK) Royal National Institute of Blind People (RNIB) Clear Print Guidelines are available to support the development of documents for visually impaired people (251). We conducted a needs assessment exercise to help design an exercise manual to meet the needs of visually impaired frail older people.

3.12 Methodology

We conducted a focus group meeting with frail older people at Westbourne Green Community Hospital, a residential intermediate care

site in Bradford where therapy-based rehabilitation typically follows an acute illness prior to return home. To develop greater insight we attempted to identify a range of participants with and without visual impairment to provide a range of views on appropriate provision of information. Written, informed consent was taken from all participants. Full ethics approval was given by Bradford Research Ethics Committee (REC reference 09/H1302/55).

Sample pages from four example exercise manuals were presented to the group and are available in appendix 4. The four exercise manuals were deliberately chosen as they had all been designed for use by older people but incorporated different page layouts, font types, text sizes, illustrations and photographs. Different types and amounts of colour and contrast were also used in the example exercise manuals. All four manuals were freely available and downloaded from the internet. Although the design of the exercise manuals was the main focus of the meeting, the clarity of the language used throughout the text was also discussed.

Example 1 was a patient handout from the American Geriatrics Foundation for Health in Aging (252). The example used size 14 Times New Roman font with no illustrations. The example was orientated in portrait layout.

Example 2 was a patient handout from horizonmedtech (253). The example used size 10 Arial font with small diagrams. The example was orientated in portrait layout.

Example 3 was a falls prevention manual from AgeUK (254). The example used size 25 Helvetica font with large black and white diagrams. The example was orientated in landscape layout.

Example 4 was an exercise manual from the US Department of Health and Human Services (255). The manual used size 11.5 Helvetica font in colour with colour photographs. The example was orientated in landscape layout.

The meeting was audio-recorded and contemporaneous field notes were taken. Written, informed consent was taken from all participants. The audio-recordings and transcripts were analysed using grounded theory methods.

3.13 Results

Four frail older people took part in the focus group meeting. Two were male and two were female; the median age was 89 years (range 80 - 97 years).

Participant one was a 97 year old lady with relatively good vision requiring only the occasional use of reading glasses.

Participant two was an 89 year old gentleman with an unspecified refractive error who wore bifocals for general purposes and had a pair of reading glasses that he used less frequently.

Participant three was an 80 year old gentleman with relatively good vision who did not use glasses. However, his wife had ARMD requiring corrective aids for reading, providing him with important insight into the needs of visually impaired older people.

Participant four was an 88 year old lady with age-related macular degeneration (ARMD) (wet in one eye and dry in the other) requiring treatment with anti-vascular endothelial growth factor injections. She wore glasses for general purposes and had a magnifying glass at home to help with reading.

3.13.1 General problems as a result of visual impairment

Participants with visual impairment reported a range of general problems as a result of poor vision, including reading print in magazines, identifying numbers on the telephone and reading subtitles on the television. Illustrative comments describing the difficulties are provided below.

> "Sometimes you think (when you're reading text you get) a false impression, it's something different to what it is and it's a bit difficult...it's all disorientated, like when you look at a window and the straight lines are not straight, they're all diddly." (participant 4. 88 year old female with age-related macular degeneration)

> "She can't watch telly as good and things are blurry." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration)

> "Yeah, the subtitles, she finds that awkward. It sort of blurs." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration). "Small… I don't know if your wife experiences that, but I do, (the subtitles are) all small." (participant 4. 88 year old lady with age-related macular degeneration). "Yes, she sometimes moans about the size of them, yes, as though it's shrunk." (participant 3).

"She gets very uptight about it, she can’t thread a needle and things like that." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration).

"Oh, she can’t dial the phone...(the numbers aren’t) plain enough, you know." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration).

3.13.2 Black and white, plain and simple

A key theme emerging from the discussion of the four examples was a preference for black text on a white background using a plain font. A size 14 font was considered by participants to be adequate although a larger font was preferred. Participants expressed a strong preference for the use of simple language without jargon. Diagrams or photographs were considered to help clarify the text explanations. Participants expressed different views regarding use of colour text. Those with better vision tended to be more open to the use of colour, as long as it wasn't overdone, whereas those with visual impairment found colour text more difficult to read, and could be distracted by its use. Illustrative comments are provided.

"Simple and plain. A decent size print." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses).

"I'd prefer to see everything on there for us to read in black and white; plain, what you can see and understand." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses).

"I think I'd rather have black and white." (participant 1. 97 year old lady with relatively good vision requiring only the occasional use of reading glasses).

"A bit colour is nice I think...If it's not overdone, yes...when you get blue, blue printing on a red background, that's no good." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration).

"Well, if you can see (the picture) just as plain or plainer in black and white, and colour tends to distract you." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses)

"I find (the diagrams) very good, they're black and white, aren't they?." (participant 4. 88 year old female with age-related macular degeneration)

Each of the four examples is discussed in turn, with illustrative comments provided.

3.13.2.1 Example 1

The size 14 font used in example 1 was considered to be adequate for participants, although the exercise instructions were felt to be unclear. Participants identified that the addition of diagrams would help clarify the text descriptions. Illustrative comments are provided below.

"Oh, the writing's okay yeah, I can read the writing through my bifocals, but I could read it better with my reading glasses." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses)

"Well, I've got to go back and read it again. I follow it now, but first time through, I didn't get it." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration).

"Little diagrams would be a big help as well." (participant 3. 80 year old male with relatively good vision but whose wife has age-related macular degeneration).

3.13.2.2 Example 2

Although three of the participants found the size 10 font in example 2 relatively comfortable to read, the participant with ARMD found it too small and had to strain to read the text. The participant whose wife has ARMD agreed that some people with visual impairment would likely have difficulty reading the text. There was a general consensus that black print on a white background is best and that, for example, white on blue (which was used in the heading of the example) is difficult to read as it doesn't stand out. Illustrative comments are provided.

"No, I have to strain a bit, I can’t see what it says there." (Participant 4, 88 year old lady with ARMD)

"The black on the white is the best." (Participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses)

3.13.2.3 Example 3

Participants expressed a strong preference for example 3. All participants found the large, black and white size 25 font easy to read and felt that the diagrams were a helpful addition. Participants found the exercise instructions clear and easy to understand. Although one participant gave a slight preference for the landscape orientation of example 3, it was difficult to determine whether this was a reflection of the general preference for the design of this example. Illustrative comments are provided below.

> "Yeah, now that is good, black on the white background, you can see that." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses).

> "You can see everything no problem. Even with bad eyesight." (participant 3. 80 year old male with relatively good vision whose wife has age-related macular degeneration). **(in reply)** "As soon as you look at it. As soon as you look at it." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses).

> "I find them very good, they're black and white, aren't they?" (participant 4. 88 year old lady with ARMD).

"Yeah, I think that's alright, I think that's a good illustration, the heels are raised." (participant 1. 97 year old lady with relatively good vision requiring only the occasional use of reading glasses).

3.13.2.4 Example 4

The participant with ARMD found the size 11.5 font a bit difficult to read, particularly when a different colour text was used. The text instructions were considered to be relatively clear. Participants found the photographs helpful but felt that the green background did not provide the right amount of contrast, which made it more difficult to understand the exercise. One participant commented that when there was more than one photograph used, it would be clearer if the photographs were numbered sequentially. Comments are provided below.

"Can I read it though? I'm not sure...It's a bit difficult." (participant 4. 88 year old lady with ARMD).

"I don't care for the green." (participant 4. 88 year old lady with ARMD).

"Well it's easy to follow what they're getting at (in the explanations), yes, it's alright." (participant 1. 97 year old lady with relatively good vision requiring only the occasional use of reading glasses). **(in reply)** "Yes, it's plain enough that is." (participant 3.

80 year old male with relatively good vision whose wife has age-related macular degeneration).

"Everybody can understand that by looking at (the photograph)." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses).

"If they try and make them interesting by changing colours, that's no good, you want to stick to something you can read and understand, black and white." (participant 2. 89 year old male with a refractive error who wears bifocals for general purposes and reading glasses).

3.14 Discussion

The needs of those who are visually impaired should always be considered when designing documents and providing information to frail older people. Our needs assessment exercise has identified that, when designing an exercise manual, frail older people prefer a minimum of size 14 font and, if possible, should be provided with a text size in excess of this. Black text on a white background is preferred, and some combinations of text colours (for example white on blue, red on blue) can be more difficult to read. Visually impaired frail older people may have greater difficulty interpreting colour and emphasis should be placed on

ensuring adequate contrast between different colours. Exercise descriptions should be as plain and simple as possible.

The results of our needs assessment exercise agree broadly with the RNIB Clear Print Guidelines, which advise that when designing documents for visually impaired people text size should be 12-14 point (preferably 14 point); text layout should be kept clear, simple and consistent; the contrast between the text and background should be as high as possible and that any information conveyed in colour or through images should also be described. The results of this needs assessment exercise will help improve the provision of information to frail older people in the HOPE manual.

3.15 Section 3. Delphi consensus process

3.16 Background

Consensus methods are a means of assessing the level of agreement between experts or lay people about a specific issue (256). The Delphi process is a consensus method that involves expert participation and follows a series of ordered rounds (234). Two rounds of a Delphi process were used in the development of a home-based exercise intervention for frail older people in preparation for testing in a pilot randomised controlled trial.

3.17 Methodology

3.17.1 Round one

Preliminary results from the modelling exercise (section 1) were analysed to identify emerging findings and key points to inform a questionnaire to assess the level of agreement with a series of key statements regarding the development of a home-based exercise intervention for frail older people (234).

3.17.2 Round two

In round two, the experienced healthcare professionals who participated in the focus group meetings were contacted by email and asked to provide responses to the key statements in the questionnaire developed following round 1. Responses were assessed using a nine-point Likert scale (1 = strongly disagree, 9 = strongly agree). Free text responses to the ten key points were also sought. An example questionnaire is provided in appendix 2.

Written, informed consent was taken from all participants. Full ethics approval was given by Bradford Research Ethics Committee (REC reference 09/H1302/55).

3.18 Results

Seven experienced healthcare professionals (one head of therapy services, one physiotherapy clinical coordinator for older people, three community physiotherapists and two community matrons) took part in the Delphi process.

3.18.1 Round one

The key themes of 'wanting to keep going' and 'managing to keep moving', along with the important constraints and motivational factors identified, were incorporated into the questionnaire.

3.18.2 Round two

Responses from six participants were received in round two. The results are summarised in table 3.1.

Statement number	Statement	Mean agreement, Likert score (standard deviation)
1	There is a large amount of variation in the functional abilities of frail older people living at home	8.2 (1.0)
2	Thought needs to be given to this variation when designing an exercise programme to improve the functional abilities of frail older people living at home i.e. a 'one size fits all approach' is inappropriate	8.0 (1.1)
3a	Older people are commonly limited by lower limb weakness	7.8 (1.2)
3b	Older people are commonly limited by poor postural flexibility/stability	8.5 (0.6)
4	These limitations are often expressed functionally by difficulty in standing from a chair and difficulty climbing stairs	8.0 (0.9)
5	Older people will require face-to-face contact on more than one occasion to help learn a structured exercise programme and improve compliance	8.3 (0.8)
6	The exercise programme needs to be simple	8.2 (1.0)
7a	It is important to include goal setting in the exercise programme	7.5 (1.4)
7b	It is important to monitor success/benefit throughout the exercise programme	8.0 (0.9)
7c	It is important to allow participants to advance during the exercise programme	7.7 (1.0)
8a	Key perceived barriers to participation are likely to be respiratory problems	7.0 (2.1)

8b	Key perceived barriers to participation are likely to be joint stiffness/joint pain	7.8 (1.0)
8c	Key perceived barriers to participation are likely to be low mood	7.3 (1.6)
9	Flares of chronic medical diseases may impact on participation in the exercise programme	7.5 (1.6)
10a	Potential measures to improve involvement/ compliance include allowing adaptation to the exercise programme, i.e. if a participant is feeling unwell then they should complete the warm-up exercises only	7.3 (1.6)
10b	Potential measures to improve involvement/ compliance include attempting to incorporate the programme into normal daily routine	8.7 (0.5)
10c	Potential measures to improve involvement/ compliance include making the programme meaningful to the individual	8.7 (0.5)
10d	Potential measures to improve involvement/ compliance include engaging with & involving family/carers	8.3 (0.5)
10e	Potential measures to improve involvement/ compliance include using different levels of exercise (e.g. chair based/standing) depending on the ability of the individual	8.3 (0.5)

Table 3.1. Agreement with a series of key statements in round two of a Delphi consensus process.

Relatively strong agreement with all key points was recorded (median 8.0, range 7.0 - 8.7). Lowest mean agreement was recorded regarding statements 8a (A key perceived barrier to participation is likely to be respiratory problems), 8c (A key perceived barrier to participation is likely to be low mood), and 10a (Potential measures to improve involvement/compliance include allowing adaptation to the exercise programme). Highest mean agreement was recorded regarding statements 3b (Older people are commonly limited by poor postural

flexibility/stability), 10b (Potential measures to improve involvement/compliance include attempting to incorporate the programme into normal daily routine) and 10c (Potential measures to improve involvement/compliance include making the programme meaningful to the individual). As there was relatively strong agreement with all the key points identified, it was considered that a third round of the consensus process would unlikely be beneficial.

3.19 Discussion

Two rounds of a Dephi consensus process have identified relatively strong agreement with a series of key statements regarding development of the HOPE programme. The results of the consensus process provide greater insight into engaging frail older people in exercise by identifying the important motivational factors and common barriers to participation in exercise and will be incorporated into the design of the HOPE programme.

3.20 Section 4. Behaviour change techniques

It is recognised that people can contribute to their overall health and well-being by adopting or avoiding certain health behaviours. Choice of health behaviour is influenced by multiple factors, including personality, cognitive and socioeconomic factors. To facilitate health behaviour change, a series of theoretical frameworks have been developed that consider these important factors (235). These frameworks have been incorporated into a wide range of health interventions, including interventions to increase physical activity in adults (257). In addition to considering these frameworks when developing health interventions it has been proposed that the individual elements of interventions, training and supervision of intervention providers, treatment delivery and treatment adherence should be reported by researchers, to aid in the identification of successful behaviour change techniques.

Importantly, behaviour change theories rarely specify techniques to change behaviour (258). Recent attempts have been made to develop a reliable, standardised taxonomy of behaviour change techniques (BCTs) used in interventions (259). This taxonomy both details behaviour change techniques and maps these onto existing theory. It is anticipated that this standardised and reliable taxonomy will facilitate identification of BCTs incorporated into successful interventions to aid in the application of evidence based behaviour change.

A summary of this taxonomy is provided in table 3.2. The 26 BCTs identified reflect a range of theoretical frameworks, including the information-motivation-behavioral skills model (IMB); theory of reasoned action (TRA); theory of planned behavior (TPB); social-cognitive theory (SCogT); control theory (CT) and operant conditioning (OC).

Behaviour change technique (theoretical framework)	Definition
1) Provide information about behaviour-health link. (IMB)	General information about behavioural risk, for example, susceptibility to poor health outcomes or mortality risk in relation to the behaviour
2) Provide information on consequences. (TRA, TPB, SCogT, IMB)	Information about the benefits and costs of action or inaction, focusing on what will happen if the person does or does not perform the behaviour
3) Provide information about others approval. (TRA, TPB, IMB)	Information about what others think about the person's behaviour and whether others will approve or disapprove of any proposed behaviour change
4) Prompt intention formation. (TRA, TPB, SCogT, IMB)	Encouraging the person to decide to act or set a general goal, for example, to make a behavioural resolution such as "I will take more exercise next week'
5) Prompt barrier identification. (SCogT)	Identify barriers to performing the behaviour and plan ways of overcoming them
6) Provide general encouragement. (SCogT)	Praising or rewarding the person for effort or performance without this being contingent on specified behaviours or standards of performance
7) Set graded tasks. (SCogT)	Set easy tasks, and increase difficulty until target behaviour is performed
8) Provide instruction. (SCogT)	Telling the person how to perform a behaviour and/or preparatory behaviours
9) Model or demonstrate the behaviour. (SCogT)	An expert shows the person how to correctly perform a behaviour, for example, in class or on video
10) Prompt specific goal setting. (CT)	Involves detailed planning of what the person will do, including a definition of the behaviour specifying frequency, intensity, or duration and specification of at least one context, that is, where, when, how, or with whom
11) Prompt review of behavioural goals. (CT)	Review and/or reconsideration of previously set goals or intentions
12) Prompt self-monitoring of behaviour. (CT)	The person is asked to keep a record of specified behaviour(s) (e.g., in a diary)
13) Provide feedback on performance. (CT)	Providing data about recorded behaviour or evaluating performance in relation to a set standard or others' performance, i.e., the person received feedback on their behaviour
14) Provide contingent rewards. (OC)	Praise, encouragement, or material rewards that are explicitly linked to the achievement of specified behaviours
15) Teach to use prompts or cues. (OC)	Teach the person to identify environmental cues that can be used to remind them to perform a behaviour, including times of day or

	elements of contexts
16) Agree on behavioural contract. (OC)	Agreement (e.g., signing) of a contract specifying behaviour to be performed so that there is a written record of the person's resolution witnessed by another
17) Prompt practice. (OC)	Prompt the person to rehearse and repeat the behavior or preparatory behaviours
18) Use follow-up prompts.	Contacting the person again after the main part of the intervention is complete
19) Provide opportunities for social comparison. (SCompT)	Facilitate observation of nonexpert others' performance for example, in a group class or using video or case study
20) Plan social support or social change. (social support theories)	Prompting consideration of how others could change their behaviour to offer the person help or (instrumental) social support, including "buddy"systems and/or providing social support
21) Prompt identification as a role model.	Indicating how the person may be an example to others and influence their behaviour or provide an opportunity for the person to set a good example
22) Prompt self-talk.	Encourage use of self-instruction and self-encouragement (aloud or silently) to support action
23) Relapse prevention. (relapse prevention therapy)	Following initial change, help identify situations likely to result in readopting risk behaviours or failure to maintain new behaviours and help the person plan to avoid or manage these situations
24) Stress management (stress theories)	May involve a variety of specific techniques (e.g., progressive relaxation) that do not target the behaviour but seek to reduce anxiety and stress
25) Motivational interviewing	Prompting the person to provide self-motivating statements and evaluations of their own behaviour to minimize resistance to change
26) Time management	Helping the person make time for the behaviour (e.g., to fit it into a daily schedule)

Table 3.2. A summary of behaviour change techniques and illustrative theoretical frameworks.

IMB, information-motivation-behavioral skills model; TRA, theory of reasoned action; TPB, theory of planned behavior; SCogT, social-cognitive theory; CT, control theory; OC, operant conditioning (259).

A brief description of each of the theoretical frameworks is provided below.

3.20.1 Information-motivation-behavioural skills model

The IMB model was first described as a conceptualisation of AIDS preventive behaviour (260). The model asserts that risk behaviour change is a function of people's information about a health condition, motivation to reduce risk and their behavioural skills for performing the necessary tasks for risk reduction.

3.20.2 Theory of planned behaviour/theory of reasoned action

The TPB is derived from the earlier TRA and both are considered to be deliberative processing models implying that attitudes and behaviours are constructed following careful consideration of available information (261-263). The TPB asserts that behaviour is determined by both the level of intention to engage in the behaviour and perception of control over performance (261).

3.20.3 Social cognitive theory

SCogT identifies that behavioural change is achieved through a personal sense of control; if people believe that they have the capability to address, for example, a health problem they become more willing to engage in behaviour change and develop a commitment to the decision (264).

3.20.4 Control theory

CT is based on the concept of a behaviour feedback loop and asserts that behaviour change is most likely if feedback is provided alongside comparison with behavioural target(s) and by individualised action plans (258, 265).

3.20.5 Operant conditioning

OC is based on the principle that behaviour is modified due to the susceptibility of an individual to behavioural reinforcement by particular consequences, which can be positively or negatively reinforcing (266).

3.21 Evidence for behaviour change techniques in the development of exercise interventions for frail older people

There is currently no evidence-based guidance for the application of BCTs in the development of home-based exercise interventions for frail older people. There is, however, guidance for the use of BCTs derived from trials conducted in the general adult population. A 2005 UK Health Development Agency review of a series of systematic reviews and meta-analyses identified that interventions based on BCTs and tailored to individual needs are associated with longer-term changes in behaviour (267). Furthermore, trials that incorporated regular contact with an

exercise specialist were associated with sustained changes in physical activity. Both home-based and group based sessions appeared to be equally effective. Use of telephone support and exercise log-books were also identified in successful interventions.

Although evidence regarding the application of particular behaviour change theoretical frameworks in the development of home-based exercise interventions for frail older people is also lacking, the social cognitive model of behaviour change has previously been shown to successfully increase physical activity participation in adults (259, 268-270).

3.22 Discussion

Although there is currently an absence of evidence-based guidance regarding the application of BCTs in the development of home-based exercise interventions for frail older people, certain BCTs have been more frequently found in effective community-based physical activity interventions in adults. This indirect evidence, in conjunction with the recently published taxonomy of behaviour change techniques outlined above, will help inform the incorporation of BCTs into the HOPE programme.

4 Chapter 4. The HOPE programme

The HOPE programme has been developed by synthesising information from the four key domains outlined at the start of Chapter 3; the systematic literature review; the process of intervention modelling work incorporating a series of multiperspective focus group meetings, an information provision needs assessment exercise and a Delphi consensus process; the review of behaviour change techniques and the review of international consensus guidelines on the development of exercise interventions for older people.

4.1 How the information from the four key domains was synthesised together

Emerging findings from the four key domains were presented by myself to the members of the HOPE study steering group at monthly meetings. The steering group members were; Professor John Young, Professor of Elderly Care Medicine, Academic Unit of Elderly Care & Rehabilitation, University of Leeds; Professor Anne Forster, Professor of Stroke Rehabilitation, Academic Unit of Elderly Care & Rehabilitation, University of Leeds; Dr Sally Barber, Senior Research Fellow & Exercise Physiologist, Academic Unit of Elderly Care & Rehabilitation, University of Leeds; Dr Louise Johnson, Senior Lecturer in Physiotherapy, School of Health Studies, University of Bradford and Dr Alison Pighills,

Rehabilitation Projects Manager, NHS Bradford & Airedale. The emerging findings were discussed in detail and consensus was reached regarding the key aspects of the HOPE programme, including the key exercises to be included, the intensity (frequency & duration) of the intervention and the proposed physiotherapist timeline. Any disagreements were resolved by group consensus.

A draft HOPE manual was then circulated to members of the HOPE study steering group by email. The draft HOPE manual was further refined through discussion at subsequent steering group meetings to improve the clarity of general instructions to participants and text descriptions of exercises. Expert validation was achieved at a further group meeting following email circulation of the draft HOPE manual and physiotherapy timeline to the Bradford Teaching Hospitals NHS Foundation Trust therapy directorate team who took part in the focus group meetings. The feasibility of delivery of the HOPE programme was confirmed through discussion with Jill Gregson, head of therapy services at Bradford Teaching Hospitals NHS Foundation Trust and Phil Wright, Physiotherapy Clinical Coordinator for Older People at Bradford Teaching Hospitals NHS Foundation Trust.

A complete description of the HOPE programme, including behaviour change strategies that have been incorporated into the intervention, is provided below.

4.2 Description of the HOPE programme

The HOPE programme is a 12 week progressive exercise intervention that is presented to participants in an exercise manual and delivered by trained community-based physiotherapists from Bradford Teaching Hospitals NHS Foundation Trust. The manual contains five sections; 1) information, 2) safety tips, 3) good posture, 4) exercises and 5) staying on track. The exercises have been selected to target the physical limitations and ADL difficulties identified during the modelling phase, supported by the UK national research questionnaire literature and Delphi consensus process. To account for the diversity of our participant group, the HOPE programme is graded into three levels. Participants are stratified to the appropriate level using the baseline timed-up and go test (TUGT) (246). Those who take 30 seconds or more to complete the TUGT are stratified into level 1; those who take between 20-29 seconds are stratified into level 2 and those who take less than 20 seconds are stratified into level 3. The complete manuals for each of the three levels of the HOPE programme are included in the supplementary material CD at the back of this thesis.

All of the exercises are easy to learn, require no special equipment and can be performed without professional supervision. The exercises for each level of the programme (Level 1, 2 and 3), their purpose (to improve strength, mobility, balance or aerobic capacity) and their functional

relevance (e.g. to improve standing up from a chair) are provided in table 4.1.

Exercise	Level	Purpose	Functional relevance
Breathing warm up 	1, 2, 3	A preparatory exercise to increase lung capacity	Reduce shortness of breath
Sitting-up 	1, 2, 3	Trunk/abdominal strength	Stair climbing, standing up from a chair, walking, balance
Spine rotation 	1, 2, 3	Trunk mobility	Washing and dressing, reaching for something on a shelf, stair climbing
Armchair rise – arm strength 	1	Upper body strength	Standing up from a chair, lifting/carrying household objects
Leg kicks 	1	Lower body strength	Standing up from a chair, walking *
Toe-heel pointing 	1	Lower body strength	Walking, stair climbing *
Marching 	1P, 2	Lower body strength	Standing from a chair, stair climbing *
Standing arm raises (for 30 seconds) 	1P	Upper body strength and mobility and balance	Reaching for something on a shelf, lifting/carrying household objects, washing and dressing falls prevention

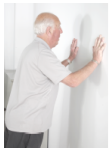
Armchair rise – arm and leg strength 	2	Upper and lower body strength	Walking, stair climbing, standing up from a chair, lifting/carrying household objects
Calf raises 	2	Lower body strength and balance	Walking and stair climbing
Leg swing back 	2P	Lower body strength and hip mobility	Standing up from a chair, dressing*
Side stepping 	2P	Balance	Falls prevention
Chair rise 	3	Lower body strength	Walking, stair climbing, standing up from a chair
Wall press-up 	3	Upper body strength and mobility	Lifting/carrying household objects, washing and dressing
Single foot calf raise 	3	Lower body strength	Walking and stair climbing
Leg back swing and side raise 	3P	Lower body strength and hip mobility	Standing from a chair, dressing *
Stand on one leg 	3P	Balance	Falls prevention
Walking toe to heel 	3P	Balance	Falls prevention
Aerobic exercises 	3P	Aerobic	Sustaining engagement in physical activities *

Table 4.1. Exercises included in the three levels of the HOPE programme.

P, progression exercise; * may also reduce arthritic pain at the mobilized joint. Copyright © 2011.

At the beginning of the intervention participants are requested to perform five repetitions of each exercise in the routine. This progresses to 10 and then 15 repetitions as performance improves. The exercise routine takes less than 15 minutes to complete, and participants are requested to complete the routine 3 times a day on 5 days of the week.

A physiotherapist timeline for the HOPE programme is provided in appendix 5. Participants receive weekly support from physiotherapists through either a face-to-face home visit or telephone call. If participants are coping well with the exercises they are encouraged to progress within the programme. Progression is by increasing repetitions, introducing new exercises or advancing to the next level of the HOPE programme. Gentle aerobic exercise is incorporated as a progression exercise at Level 3 of the HOPE programme to introduce the concept of aerobic exercise to the more physically able participants.

4.2.1 Strategies to support behaviour change

The HOPE programme is based predominantly on the social cognitive model of behaviour change as a theoretical framework, as this has previously been shown to successfully increase physical activity participation in adults (259, 268-270). Details of the behaviour change techniques and how they are incorporated into the HOPE programme are shown in Table 4.2.

Behaviour change technique (theoretical framework)	**How the technique is in the intervention**
Provide information on consequences (SCogT)	Information given about the value of exercise for health in older age
Provide general encouragement (SCogT)	Praise and encouragement given by physiotherapists weekly during either a home visit or telephone call
Set graded tasks (SCogT)	Opportunities to progress (increased repetitions, addition of progression exercises, advancing to the next level of the programme) are discussed between participant and physiotherapists and an individual progression plan is agreed upon
Provide instruction (SCogT)	Each participant receives a HOPE programme manual that gives instructions for the programme and describes in written and pictorial format how to perform each exercise. Physiotherapists also provide instruction during home visits and telephone calls
Model or demonstrate the behaviour (SCogT)	Physiotherapists demonstrate how to correctly perform exercises during home visits
Prompt specific goal setting (CT)	The physiotherapists facilitates the participant to set specific functional improvement goals
Prompt self-monitoring behaviour (CT)	The participant is asked to keep a record of which days they do their exercises on and how many times they complete the routine that day

Prompt practice (OC)	Participants are provided with a HOPE programme fridge magnet to prompt them to perform their exercise routine
Relapse prevention	Three “gentle exercises” are provided in the HOPE manual for participants to complete if they are “having a bad day” (this was identified in focus groups as a situation likely to result in failure to maintain the exercise programme)

Table 4.2. Behaviour change techniques used in the HOPE programme.

Techniques and theoretical frameworks were defined using (259). SCogT, social cognitive theory; CT, control theory; OC, operant conditioning.

4.3 Discussion

The HOPE programme has been developed using rigorous research methodology that has assimilated evidence from RCTs, international consensus guidelines and considerable input from frail older people and expert healthcare professionals. The evaluation of the HOPE programme in a pilot RCT (the HOPE trial) will be discussed in Chapter 5.

5 Chapter 5. Evaluation of the Home-Based Older People's Exercise (HOPE) programme: the HOPE trial

5.1 Background

The MRC framework for developing and evaluating complex health interventions stresses the importance of piloting and feasibility work prior to testing an intervention in a definitive trial (233). This chapter describes the evaluation of the HOPE programme in a pilot RCT.

5.2 Objectives

To conduct a pilot RCT to:

1) explore methods to identify frail older people in community settings;

2) assess the acceptability of the HOPE programme to frail older people;

3) test for a preliminary estimate of effectiveness;

4) test the feasibility of recording data to identify the therapy resources required to deliver the HOPE programme;

5) gather data to inform the design of a definitive clinical trial

5.3 Design

The HOPE trial design and methodology is based on the MRC framework (233) and international consensus guidelines for the design of RCTs of interventions to prevent functional decline and disability in frail older people (232). The international consensus guidelines provide recommendations to address the major potential challenges that should be considered when designing RCTs of interventions for frail older people and are summarised in table 5.1. These potential challenges and recommendations have informed the development of the HOPE trial and have been incorporated into the trial design where possible.

Challenges	Recommendations
Standard criteria for physical frailty are lacking	Operationalise variables in the domains of mobility, nutrition, and body composition. Justify the specific criteria used in the trial
Enrolling the most appropriate study population may be complex and expensive	Use a multistage selection process: 1) Exclude the ‘‘robust.’’ 2) Identify those who are frail. 3) Identify subset according to specific domains of physical frailty.
Excessive exclusions may reduce generalisability	Design studies with the idea of enabling participation. The principal exclusion criteria should be factors that prevent participation. Avoid exclusions for comorbidity. Ascertain the level of cognitive impairment incompatible with participation in specific interventions.
Inclusion and exclusion of frail older persons from trials raise ethical concerns	Make explicit the procedures used for consenting participants. Provide multiple methods to explain the study to the

	participants and involve a surrogate when needed. Discuss ethical issues when reporting results.
Assessing disability through self-report may be problematic	Limit self-report to primary outcomes that are ‘‘hard’’ measures of disability such as activity of daily living disability, mobility disability. Standardize disability questions and responses and provide continuing, intensive training to interviewers. Collect objective measures of physical function and proxy information in parallel. Make the outcome less sensitive to random fluctuations (e.g., defining disability as ‘‘lasting more than 3 months’’ or targeting ‘‘multiple falls’’) Include mortality in the primary outcomes.
The mechanism by which the intervention prevents disability may be unclear	Use as secondary outcomes physiological or functional measures that are in the theoretical pathway between the intervention target and the disability outcome.
Improvements in functional status may not translate into well-being and quality of life	Use secondary outcome measures that assess perceived well-being and factors,such as somatic symptoms, that are important for quality of life in frail older persons. Consider global impression.
Avoid attrition and competing morbidity	The expected mortality and dropout rates should be incorporated into sample size calculations. Adherence rates can be improved by designing interventions feasible by most, allowing flexible time-frame for follow-up interviews, providing a comfortable environment, prioritizing safety, providing transportation, establishing a good relationship with family or caregivers, preplanning alternatives to full clinic visits

	(e.g., shorter home visits, telephone calls).

Table 5.1. Major challenges and recommendations involving randomised controlled trials of disability prevention in frail older persons.

Adapted from (232).

The HOPE trial is a two arm, assessor blind pilot RCT to assess the effectiveness of an exercise intervention (the HOPE programme) designed to improve the mobility and functional abilities of frail older people living at home, compared with usual care. The 12 week HOPE programme is delivered to trial participants by community-based therapists from Bradford Teaching Hospitals NHS Foundation Trust. Follow-up is at 14 weeks post randomisation.

5.4 Methodology

5.4.1 Setting

Bradford, UK; a post-industrial ethnically diverse northern city with a population of 350,000 people.

5.4.2 Methods of recruitment & inclusion criteria

Those eligible for inclusion were frail older people. A research question under investigation in this pilot trial was to identify the most efficient

recruitment method(s) for this hard to reach group of people. Multiple recruitment sources were therefore used to identify frail older people:

1. Older people living at home and under the care of a case manager (CM) in Bradford, UK. CMs are experienced nurses specifically trained in the management of long term conditions and provide nurse-led case management working alongside primary care teams and social service staff. The case management service has been developed nationally with a specific policy objective of reducing acute hospital admissions for people with multiple long-term conditions, who are more likely to be frail. There are a number of models of case management within the Bradford Primary Care Trust (PCT), including case management by Community Matrons and Advanced Nurse Practitioners. CMs were identified with the assistance of the NHS Bradford & Airedale General Services Management Team following a series of educational meetings.

2. Older people who were housebound, defined as being unable to leave the house without the assistance of another person. Housebound older people were identified through Read code searching of general practitioner (GP) registers of National Institute for Health Research (NIHR) 'Research Ready' GP practices in Bradford, UK; social services sites providing day centre and

respite care in Bradford, UK and at discharge from intermediate care hospitals in Bradford, UK.

The initial method of approach for those identified through GP registers of NIHR Research Ready practices was by letter from the GP practice. The initial method of approach for potential participants identified by case managers, social services sites providing day centre and respite care and intermediate care hospitals was by face-to-face or telephone contact from the healthcare professional or senior member of social services staff who was co-ordinating care.

5.4.3 Exclusion criteria

1. Unable to stand and walk independently
2. Current participation in an alternative exercise programme (e.g. falls prevention programme, pulmonary rehabilitation)
3. Registered blind
4. Poorly controlled angina
5. Another member of the household already in the HOPE trial
6. Severe dementia
7. Receiving palliative care

5.4.4 Sample size

A successful pilot RCT provides important information regarding process, resource, management and scientific data (271). To provide useful process, resource, management and scientific data a recruitment target of 100 participants (50 per group) was set. A formal sample size calculation was not done because the estimates of effect size and variance obtained from the pilot RCT will be used to inform the power calculation for a future definitive RCT.

This pilot RCT was designed to explore:

1) Process: test feasibility of the trial and intervention e.g. trial recruitment rates, drop out rates, intervention compliance
2) Resources: record resources required to identify and gain consent from participants, time to complete study assessments, resources required to deliver the intervention
3) Management: gain insight into trial personnel and data management issues
4) Scientific: estimate intervention effect size and variance, test intervention safety

5.4.5 Randomisation

Participants underwent central, concealed randomised allocation to intervention or usual care. Participants were stratified by the baseline timed up and go test and underwent randomisation using restricted

blocks of random size with an allocation ratio of 1:1. Generation and storage of the HOPE trial randomisation sequence, and conduction of individual participant randomisation was conducted by the University of Leeds Clinical Trials Research Unit (CTRU), ensuring allocation concealment.

5.4.6 Baseline assessment

Baseline assessment was conducted by an elderly care researcher and included age, sex, cognitive assessment (Mini-Mental State Examination, MMSE), co-morbidity index (272) and the Edmonton Frail Scale (EFS), a validated and reliable measure of frailty (273). The EFS samples 10 domains, including cognitive impairment, functional ability and mobility. The maximum score is 17, which represents the highest level of frailty. The EFS demonstrates good inter-rater reliability (estimated $\kappa = 0.7$) and internal consistency (Cronbach's $\alpha = 0.62$).

Involvement in previous formal exercise programmes and the dates of any previous involvement were also recorded.

5.4.7 Primary outcome measure

1. Timed Up and Go test (TUGT) (246), measured at baseline and 14 weeks post-randomisation. The TUGT measures, in seconds, the time taken to stand up from a standard chair, walk a distance of 3 metres, turn,

walk back to the chair and sit down. A chair with armrests and a seating depth of 44-47cm is recommended. For the HOPE trial, if a chair with armrests and a recommended seating height was available in the participant's home this was used for the TUGT. If a chair with armrests and recommended seating height was not available, a standard chair with adjustable seating height was used (Prima modular shower stool with back and arms, available from Gordon Ellis & Co). A distance of 3m was measured out and, after one practice test, the participant was instructed to start the TUGT on the word 'go', at which point the stopwatch was started. The stopwatch was stopped when the participant had sat down in the chair again and the time was recorded. If the participant was unable to complete the TUGT, an *a priori* score of 300s was recorded, as this was the maximum time taken to complete the TUGT in the original validation study.

Those who complete the test in less than 20 seconds tend to be independently mobile, able to get in and out of a chair without assistance and climb stairs. Those who complete the test in 30 seconds or more tend to require assistance with getting in and out of a chair, climbing stairs and leaving the house. Those who complete the test in 20-29 seconds demonstrate greater variability in mobility, balance and functional ability (246).

The TUGT has been demonstrated to be a practical, reliable and valid measure of mobility in community dwelling older people (274). It is associated with high participation rates across this group and is therefore considered to be an appropriate measure of mobility for frail older people, including those who use a walking aid (274). The TUGT score demonstrates high inter-rater and intra-rater reliability (intraclass correlation coefficients (ICCs) 0.99 and 0.99 respectively) and correlates well with measures of gait speed, functional ability and balance. An improvement of 1.4 seconds on the TUGT (within-patient change score) has been identified as the minimum clinically important difference (MCID) (275).

5.4.8 Secondary outcome measures

1. Modified Barthel Index of activities of daily living (ADL) (194), measured at baseline and at 14 weeks post-randomisation. The Barthel Index assesses functional status on a 20 point scale by recording ability to complete ten activities of daily living; bathing, bladder function, bowel function, dressing, feeding, grooming, mobility, stairs, toilet use and transfers. Higher scores indicate greater independence. An MCID of 1.85 points has been identified, but floor and ceiling effects can limit the utility of the Barthel Index (276, 277). For the HOPE trial, self-reported Barthel Index was recorded. Where self-reported information was not possible or considered unreliable, a proxy report was sought.

2. The EuroQol Group 5-Dimension Self-Report Questionnaire (EQ-5D) (222), measured at baseline and at 14 weeks post-randomisation. The EQ-5D is a standardised measure of health utility (quality of life) comprising five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has three levels: no problems, some problems, severe problems. The scores for each of the five dimensions are combined in a five digit number representing health status that can be converted into a summary index (0 for dead, 1 for perfect health and negative values for states worse than death) using the time trade-off method (278).

3. Geriatric Depression Scale - Short Form 15 (GDS) (279), measured at baseline and at 14 weeks post-randomisation. The GDS is a screen for the presence and severity of depression in older people. It comprises 15 individual questions; a score of 0-4 indicates no depression, 5-10 is suggestive of mild depression and 11+ is suggestive of severe depression.

Recruitment rates; proportions and reasons for non-consent; protocol compliance by therapists; rates of adherence to the HOPE programme by patients; drop out rates; rates of completion of outcome measures; unscheduled admissions to hospital were also recorded, along with falls and documentation of muscle/joint pain.

It was anticipated that the main cost of the intervention would be the future therapy resources associated with delivery of the HOPE programme. To perform a formal cost-effectiveness analysis in the future definitive trial, the feasibility of collection of data to identify the therapy resources required for delivery was therefore tested. This data included time taken for each physiotherapist home visit, time for telephone consultations and travel time and was recorded by the physiotherapists who delivered the intervention.

5.4.9 Analysis plan

The exploratory nature of this pilot study requires mainly descriptive statistics and focuses on the estimation of effects sizes, 95% confidence intervals and variation estimation for planning of the future definitive trial. The baseline differences between the control and intervention groups in terms of the baseline assessment tests were compared and differences in any other potential confounding variables (age, sex, co-morbidity) were assessed.

Histograms with normal curves were plotted to assess the distribution of data for each of the primary and secondary outcome measures. Skewed data were log transformed to yield lognormal distributions.

All outcome measures were summarised and 95% confidence intervals constructed for the difference in outcomes between control and

intervention groups. Change scores were calculated by subtracting follow-up values from baseline values. As analysing change does not control for baseline imbalances because of regression to the mean (280), analysis of covariance (ANCOVA) tests were used for continuous outcomes, with adjustment for baseline values. Both adjusted and unadjusted values were tested to detect which has the smaller variance for future planning. Risk ratios with 95% confidence intervals were used for binary outcomes. Missing data were addressed by listwise exclusion.

The final intention-to-treat analysis included all randomised participants for whom the follow-up assessment of the primary outcome measure was available. The per-protocol analysis included all randomised participants who were deemed to have no protocol violations.

5.4.10 Protocol violations

Participants who were randomised to the HOPE programme (intervention) arm but did not undertake any of the HOPE programme were deemed to be protocol violations.

5.4.11 Risks

Safe exercise guidelines were followed and exercise intensity was increased gradually by therapists with experience in the delivery of exercise interventions to frail older people living at home. All potential

participants were informed of the potential risks in the participant information documents provided, so that informed consent was taken with full knowledge of potential risks. Potential risks included muscle pain, general fatigue and risk of falls.

5.4.12 Adverse events

An adverse event (AE) was any unfavourable and unintended sign, symptom, syndrome or illness that developed or worsened during the period of observation in the trial. This included:

1. Exacerbation of a pre-existing illness
2. Increase in frequency or intensity of a pre-existing episodic event or condition
3. Condition detected or diagnosed after the intervention even though it may have been present prior to the start of the trial
4. Continuous persistent disease or symptoms present at baseline that worsen following the start of the trial.

A serious adverse event (SAE) was any AE occurring following trial mandated procedures that results in any of the following outcomes:

1. Death
2. A life-threatening adverse event
3. Inpatient hospitalisation
4. A disability/incapacity

All AEs were assessed for seriousness, causality and expectedness by the trial chief investigator (AC) and recorded and closely monitored. The chief investigator was to be informed immediately following any SAE to determine causality and expectedness. Any SAE that was deemed to be directly related to the trial intervention, or suspected to be related to the trial intervention, was to be reported immediately to the ethics committee.

5.4.13 Informed consent

Informed, written consent was obtained from all trial participants by an elderly care researcher during a visit to the participant's home. Consent was in full accordance with the Mental Capacity Act 2005 (281) and International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) (282). It was emphasised that participants were free to withdraw from the trial at any time and that this will not affect the future care that they received.

5.4.14 Ethical and organisational review

The Bradford Research Ethics Committee (application number 09/H1302/55) granted ethical approval for the HOPE trial. NHS Bradford and Airedale and Bradford Teaching Hospitals NHS Foundation Trust granted NHS Research & Development (R&D) approval.

5.5 Results

A change to case manager service provision in south Bradford meant that recruitment rates were lower than anticipated, and 60 participants were recruited to February 2011. The results presented are an interim analysis of data obtained from these 60 participants. Trial recruitment is ongoing and 84 participants have now been recruited (end November 2011).

5.5.1 Trial recruitment

Between July 2010 and February 2011 a total of 264 potential participants were assessed for eligibility. Information regarding those who were excluded and the overall flow of participants through the trial is summarised in the CONSORT diagram provided below (figure 5.1).

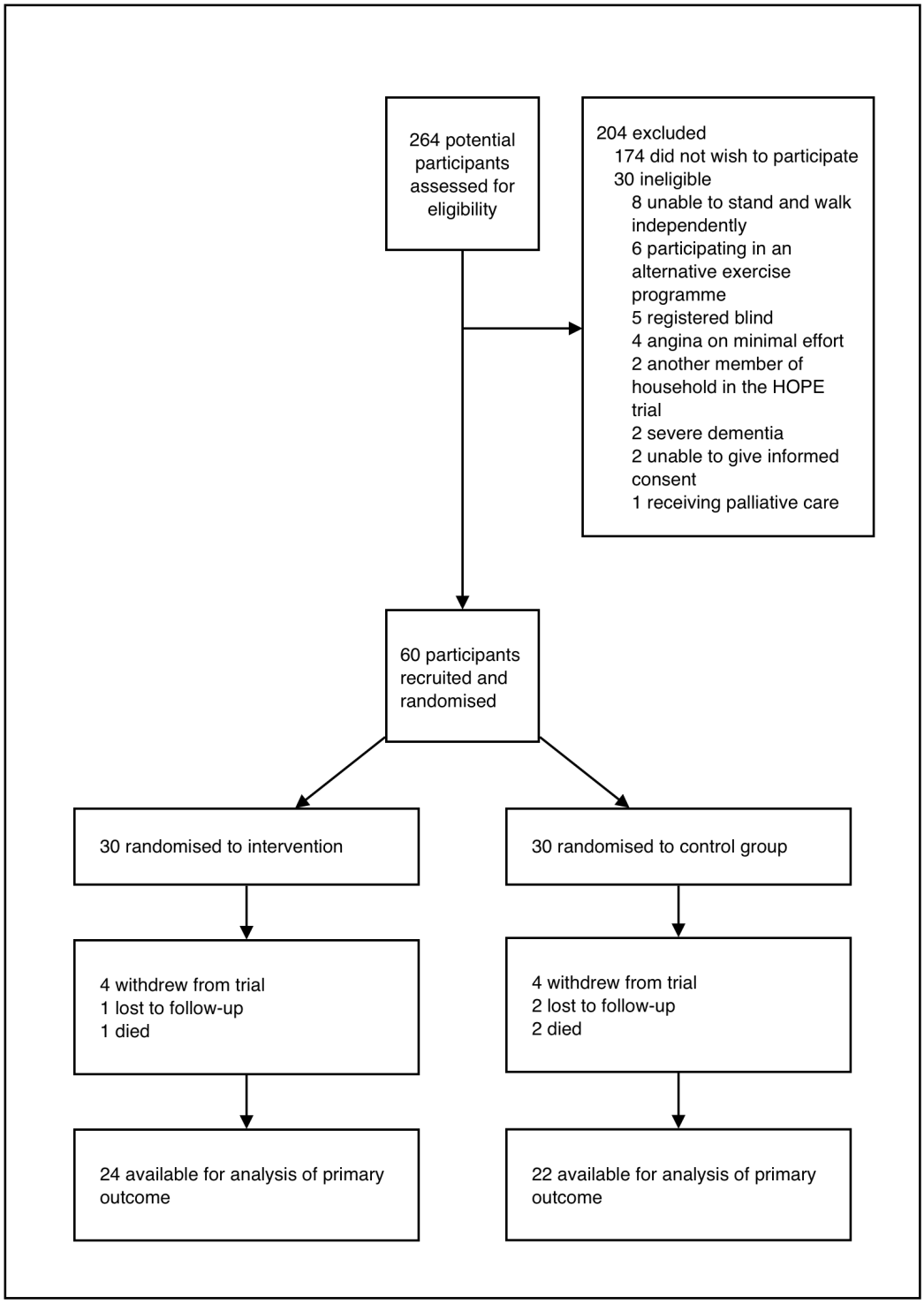


Figure 5.1. CONSORT flow diagram.

Of the 264 participants who were assessed for eligibility, 174 did not wish to participate in the trial and 30 were ineligible. A total of 60 participants (23% of those who were assessed) were successfully recruited and

randomised. Eight participants withdrew from the trial (four from each arm), three were lost to follow-up (one in the intervention group, two in the control group) and three participants died (one in the intervention group, two in the control group). None of the deaths were directly related to the exercise intervention. Follow-up information is therefore available for 46 participants (77% of those randomised).

5.5.2 Reasons given by those who did not wish to participate

A summary of reasons given by those who did not wish to participate is presented in table 5.2 and discussed below.

Reason given by those who did not wish to participate	Percentage, %
Not interested	39
Did not reply to letter	28
Already exercise	10
General ill health	8
Unable to commit	4
Felt 'too old'	3
Too much pain	2
Other	6

Table 5.2. Reasons why people did not wish to participate in the HOPE trial.

Common reasons for declining participation were lack of interest, already being engaged in regular self-directed exercise and general ill health. Less common reasons for declining participation include an inability to commit to a 12 week exercise programme, feeling 'too old' and having too much pain.

5.5.3 Recruitment rates from different sources

Information about the recruitment rates from different sources is provided in table 5.1.

Method of identification	Number approached	Number recruited	Recruitment rate
Case manager	146	47	0.32
Respite care	8	2	0.25
Day centre	46	6	0.13
Intermediate care	15	2	0.13
GP practice	49	3	0.06

Table 5.1. Recruitment rates by method of participant identification.

5.5.4 Baseline characteristics

Mean age of participants was 78 years (standard deviation, SD, 9.8 years). The majority (70%) of participants were female. Baseline characteristics were similar in the two groups, with no statistically

significant differences between the intervention and control groups (table 4.2).

The overall mean baseline Edmonton Frail Scale was 8.4 (SD 2.6), indicating that participants were relatively frail. The overall mean baseline TUGT for all participants was 48.1 seconds (SD 54.8 seconds). The mean baseline TUGT was 51.6 seconds in the intervention group and 44.5 seconds in the control group. The majority of participants in both intervention (79%) and control groups (77%) were mobile either independently or with a walking stick.

Intervention and control groups were well balanced in terms of stratification levels, with 15 participants stratified to level 1 in each group, six to level 2 in each group and nine to level 3 in each group.

Characteristic	Intervention Group (n = 30)	Control Group (n = 30)
Age - years, mean (SD)	78.8 (8.6)	77.4 (11.1)
Sex, no. (%)		
female	23 (77%)	19 (63%)
male	7 (23%)	11 (37%)
Ethnicity, no. (%)		
Caucasian	24 (80%)	24 (80%)
Asian	6 (20%)	6 (20%)

Characteristic	Intervention Group (n = 30)	Control Group (n = 30)
Living circumstances, no. (%)		
living alone	14 (47%)	13 (43%)
living with spouse/partner	11 (36%)	8 (27%)
living with family	5 (17%)	9 (30%)
Mobility aid used *, no. (%)		
independent	11 (39%)	16 (53%)
walking stick(s)	11 (39%)	7 (23%)
Zimmer frame	5 (18%)	4 (13%)
3-wheeled walker	1 (4%)	3 (10%)
Charlson comorbidity index, mean (SD)	2.6 (2.1)	3.0 (2.2)
TUGT (seconds), mean (SD)	51.6 (56.8)	44.5 (53.4)
Stratification level, no. (%)		
Level 1 (≥ 30 seconds on TUGT)	15 (50%)	15 (50%)
Level 2 (20-29 seconds on TUGT)	6 (20%)	6 (20%)
Level 3 (0-19 seconds on TUGT)	9 (30%)	9 (30%)
Edmonton frail scale, mean (SD)	8.2 (2.3)	8.5 (2.9)
Barthel index, mean (SD)	15.5 (3.7)	15.2 (4.0)
Mini-mental state examination, mean (SD)	25.9 (4.5)	24.3 (4.5)
Geriatric depression scale, mean (SD)	4.0 (2.7)	5.3 (3.1)

Table 5.2. Baseline characteristics.

There were no statistically significant differences in any of these characteristics between the intervention and control groups. Chi-square tests were used for categorical variables, t-tests were used for continuous variables.

*** - numbers do not add up to totals due to missing data**

Key: SD, standard deviation; TUGT, timed-up-and-go test

5.5.5 Time required for consent, baseline and follow-up assessments

Data was only recorded for participants who were successfully recruited. A mean time of 84 minutes (SD 23 minutes) was required for the initial consent and baseline assessment; a mean time of 49 minutes (SD 20 minutes) was required for the follow-up assessment.

5.5.6 Intervention completion rates and participant compliance

Twenty participants in the intervention group (66%) completed the 12 week HOPE programme. Six participants requested to drop out from the intervention, three participants were considerd by the physiotherapist to have alternative rehabilitation needs that were not provided by the HOPE programme and one relative requested that a participant with moderate dementia drop out of the intervention, as they were non-compliant.

Complaince diaries were returned by 16 of the 20 participants (80%) who completed the 12 week intervention. Of the 16 compliance diaries that were returned, mean diary completion (defined as the percentage of the compliance diary that was completed) was 60% (SD 41%). Mean total compliance (defined as the percentage of days that the intervention was completed three times a day over the course of the 12 week intervention) was 45% (SD 40%). Mean partial compliance (defined as the percentage of days that the intervention was completed at least once a day over the course of the 12 week intervention) was 75% (SD 34%).

5.5.7 Between group comparisons

Unadjusted and adjusted between group differences in primary and secondary outcome measures are summarised in table 5.3. Adverse outcomes are summarised in table 5.4.

5.5.7.1 Primary outcome

Although mobility had deteriorated in both groups at follow-up (intervention group mean adjusted change in TUGT -20.0s (95%CI -54.4, 14.5s), control group mean adjusted change in TUGT -36.7s (95% CI -72.8, -0.6s) there was a non-significant trend towards a clinically meaningful improved outcome in the intervention group (mean adjusted between group difference in TUGT 16.7s, 95% CI -33.3, 66.6s). Wide confidence limits indicate considerable uncertainty in this result. Two

participants in the intervention group and four participants in the control group were unable to complete the TUGT at follow-up and were hence assigned an *a priori* score of 300s. To test the contribution of these participants to the overall results a sensitivity analysis was performed whereby the data analysis was re-run with the results from these participants removed. Following the sensitivity analysis, the non-significant trend towards a clinically meaningful slower deterioration in mean TUGT in the intervention group was maintained, but diminished (mean adjusted between group difference 4.1s, 95% CI -11.9, 20.0s).

5.5.7.2 Secondary outcomes

There were no between group differences in activities of daily living, measured using the Barthel Index, quality of life, measured using the EQ5D or depression, measured using the geriatric depression scale.

5.5.7.3 Adverse outcomes

There were no differences in risk of falls (risk ratio 0.93, 95% CI 0.29, 2.93) or hospitalisation (risk ratio 0.74, 95% CI 0.14, 3.95). There were no admissions to long-term care in either group.

Outcome measure	Intervention group (mean (SD))			Control group (mean (SD))			Unadjusted between-group differences (mean (95% CI))	Adjusted between-group differences (mean (95% CI))
	Baseline	Follow-up	Change	Baseline	Follow-up	Change		
Timed-up-and-go test (s)	54.7 (60.0)	74.1 (80.8)	-19.4 (79.5)	49.8 (61.4)	87.2 (106.4)	-37.4 (89.5)	18.0 (-32.3, 68.2)	16.7 (-33.3, 66.6)
Barthel Index	15.6 (4.0)	15.3 (3.9)	-0.3 (2.4)	15.5 (4.1)	15.1 (3.5)	-0.4 (3.3)	0.1 (-1.9, 1.9)	0.2 (-1.4, 1.7)
EQ5D	0.47 (0.34)	0.43 (0.35)	-0.03 (0.32)	0.48 (0.25)	0.46 (0.27)	-0.02 (0.23)	-0.01 (-0.19, 0.16)	-0.02 (-0.18, 0.14)
GDS	4.4 (2.9)	4.4 (3.7)	0.0 (2.3)	5.7 (3.3)	5.1 (3.2)	0.6 (3.6)	-0.6 (-2.5, 1.3)	-0.15 (-2.0, 1.7)

Table 5.3. Unadjusted and adjusted between-group differences in primary and secondary outcome measures.

To control for baseline imbalances, data were adjusted using analysis of covariance (ANCOVA) tests. SD, standard deviation; CI, confidence interval; EQ5D, EuroQol 5-Dimension self-report questionnaire; GDS, geriatric depression scale.

Outcome	Intervention Group		Control Group		Risk ratio (95% CI)
	Number of participants with outcome	Number of participants in total	Number of participants with outcome	Number of participants in total	
Falls	4	19	5	22	0.93 (0.29 - 2.96)
Hospitalisation	2	19	3	21	0.74 (0.14 - 3.95)

Table 5.4. Risk of falls and hospitalisation in intervention and control groups.

CI, confidence interval.

5.5.7.4 Subgroup analyses

Participants were classified into those who were frail and those who were non-frail, using a baseline EFS $\geq$ 8 to identify frailty. For the primary outcome, there was a non-significant trend towards maintenance of mobility in those who were frail (mean adjusted between group TUGT difference 14.6s, 95% CI -60.3, 89.6s). There was no difference for those who were non-frail (mean adjusted between group difference -0.5s, 95% CI -13.9, 12.8s).

Subgroup analyses were also performed by stratification level. For the primary outcome, there was a non-significant trend towards maintenance of mobility in level 1 participants (mean adjusted between group TUGT difference 25.9s, 95% CI -47.8, 99.8s) and level 2 participants (35.2s, 95% CI -182.7, 253.1s). The wide confidence limits imply considerable uncertainty. There was a small, non-significant between group difference for level 3 participants (mean adjusted between group difference -2.9s, 95% CI -11.8, 17.5s).

5.5.7.5 Protocol violations

There was only one protocol violation and, as this participant withdrew from the trial so no follow-up data was available, a per-protocol analysis was not performed.

5.5.8 Therapy resources required

Therapy records were returned for 15 participants (50%) who were randomised to the intervention group. Median time between randomisation and date of the first visit by the physiotherapist was 16 days (range 7-44 days). Limitations of data obtained from therapy records did not permit estimates of therapy resources required for delivery of the intervention to be made.

5.5.9 Rates of researcher unblinding

Despite the use of multiple measures to maintain blinding, including clear information in the participant information leaflet, verbal information at baseline assessment and a verbal request by the research team prior to the follow-up visit, researchers were unblinded by participants during 59% of follow-up visits. Unblinding was more common when participants were in the intervention group (65%) as compared to the control group (52%). Unblinding was either by direct information from the participant or through indirect information, such as the HOPE programme manual being on display at the follow-up visit or the delivery of the HOPE programme being delayed due to unforeseen circumstances, necessitating rearrangement of the follow-up visit.

6 Chapter 6. Discussion

The HOPE programme has been evaluated in a methodologically rigorous pilot randomised controlled trial that has followed the MRC guidelines for the development and evaluation of complex interventions. The pilot trial has provided valuable process, resource, management and scientific data.

6.1.1 Process data

The HOPE trial has provided valuable process data to help inform the development of a future definitive RCT. As there is currently no simple method of identification of frail older people as part of routine care, recruitment of frail older people to the HOPE trial was particularly challenging. A number of methods to identify frail older people were adopted and, of those who were approached, approximately 1/4 were successfully recruited into the trial. Perhaps unsurprisingly, recruitment tended to be most successful when the initial approach was made face-to-face by a healthcare professional or member of the social services team who was well known to the potential participant.

Given that the trial recruited a population of frail older people at high risk of adverse outcomes, retention rates were relatively high, with only eight out of 60 participants (13%) withdrawing from the trial. Only three participants (5%) were lost to follow-up.

66% of participants completed the 12 week intervention and most participants returned the compliance diary, although of those that were returned, the completion rates were relatively low at 60%. Although mean partial intervention compliance was relatively high at 75%, total compliance was lower, with a mean of 45% suggesting that a home-based exercise intervention intensity of three times per day on five days of the week may be too much for some frail older people.

6.1.2 Resource data

Participants required considerable time for completion of the consent process and both baseline and follow-up assessments, with approximately 2 1/2 hours of face-to-face contact required. Although limitations of data from therapy records prevented estimates of resources required for delivery of the intervention, modifications have been made to the therapy record and will help facilitate ongoing collection of data.

6.1.3 Management data

The principle challenge of trial management was maintenance of assessor blinding. Assessors were frequently unblinded, both directly and indirectly, at the follow-up assessment. Measures were incorporated to attempt to maintain blinding, including clear information in the participant information leaflet and a verbal reminder prior to the follow-up

assessment. However, the presence of cognitive impairment in the frail older population can make maintenance of assessor blinding particularly challenging as there is likely to be a greater potential for participants forgetting information that has been provided to them regarding the importance of maintaining blinding. The high rates of assessor unblinding highlight the need to consider including a sham intervention when designing RCTs of complex interventions for frail older people.

The median time between randomisation and first physiotherapist visit was 16 days. A delay between randomisation and first physiotherapist visit necessitated a change to the date of participant follow-up, which had the potential to compromise assessor blinding in a small number of cases. NHS physiotherapists from Bradford Teaching Hospitals NHS Foundation Trust worked exceptionally hard to deliver the HOPE programme in addition to usual NHS commitments. To facilitate delivery of the initial physiotherapist visit and help maintain assessor blinding, consideration should be given to employment of a dedicated HOPE physiotherapist for a future definitve trial, particularly if a sham intervention is to be considered.

6.1.4 Scientific data

The pilot RCT has provided preliminary evidence that a home-based exercise intervention for frail older people is feasible, acceptable and safe. The results from the pilot RCT have demonstrated a trend towards a

clinically meaningful slower deterioration in mobility, measured using the TUGT, in the group who received the HOPE programme compared to the control group, who received usual care. Sensitivity analyses demonstrated that the trend was maintained, albeit diminished, when those who were unable to complete the TUGT at follow-up were excluded from the analysis. Subgroup analyses demonstrated that the trends were maintained in those who were frail, defined using a validated measure of frailty.

6.2 Strengths of the trial

The HOPE trial was methodologically rigorous and followed international guidelines for both the development and evaluation of complex interventions and design of randomised controlled trials for frail older people. A number of recruitment methods were used to identify frail older people for the HOPE trial. The mean age of 78 years and mean EFS score of 8.4 at baseline adds confidence that these recruitment methods were appropriate and did indeed identify older people who were frail. The earlier systematic review identified that there were no previous trials of home-based exercise interventions for frail older people that used a validated measure of frailty to select participants or stratify results. On the basis of current knowledge, the HOPE trial is the first RCT of a home-based exercise intervention for frail older people that has reported baseline frailty and stratified results using a validated frailty model.

In keeping with a successful pilot RCT, the HOPE trial has provided valuable process, resources, management and scientific data. This valuable data will inform the design of a future definitive trial and help guide the design of future RCTs of exercise interventions for frail older people.

6.3 Limitations of the trial

As a result of the considerable challenges of identifying and recruiting frail older people to the HOPE trial, recruitment rates were lower than anticipated and 60 participants were recruited to February 2011. Trial recruitment is ongoing and accrual is steadily increasing.

Although the secondary outcome measures were appropriate for a pilot RCT of a home-based exercise intervention for frail older people, it is plausible that these ordinal outcomes were not sufficiently sensitive to detect change for a trial that recorded outcomes over a 14 week period. Previous research has demonstrated that the EQ-5D may be less sensitive to change than alternative quality of life measures (283) and there is uncertainty regarding the sensitivity to change over time for the Barthel Index (284).

A further potential limitation of the trial was the high rates of assessor unblinding. These data highlight the need to consider inclusion of a sham intervention when designing RCTs of complex interventions for frail older

people, who are likely to have an increased risk of cognitive impairment, and who hence may not consistently remember the importance of maintaining assessor blinding, despite repeated reminders.

Limitations in the data required to investigate therapy resources needed for delivery of the HOPE programme meant that estimates of cost were precluded. However, the pilot trial is ongoing and a number of simple changes have increased the utility of the therapy record, helping to capture the necessary data required for cost estimates to be made.

6.4 Consideration of the results from the HOPE trial in the context of previous research

6.4.1 Potential implications of the between-group TUGT difference recorded in the HOPE trial

An adjusted between-group TUGT difference of 16.7s (95% CI -33.3, 66.6s) was recorded in the HOPE trial. It is important to identify the potential implications of a between-group TUGT difference of this magnitude. Although the TUGT demonstrates good agreement with measures of functional ability and is considered sensitive to mobility changes (246, 285, 286) there is a paucity of data regarding the potential functional relevance of changes of different magnitude. Information to aid

interpretation of the clinical relevance of differences in outcome is provided by values for the minimal clinically important difference.

6.4.1.1 The minimal clinically important difference

The minimal clinically important difference (MCID) identifies the threshold that defines when an individual (or group) has begun to experience an important improvement (287). A 2001 review identified a taxonomy of nine different methods for evaluating MCID; patient comparison to a global rating; patient conversation; clinician consensus development; clinician-led patient scenario scoring; clinician-led patient scenario comparison; clinician-led prognostic rating scale; data-driven approach; discerning important improvement criteria and achieving treatment goals (288).

A 2011 prospective cohort study compared three approaches to defining the MCID for four performance measures (including the TUGT) in 65 patients (mean age 66.5 years, SD 9.4 years) with hip osteoarthritis receiving physiotherapy treatment (275). The three approaches were all based on patient comparison to a global rating score - the Global Rating of Change Score (GRCS) (289). GRCS measured at baseline and nine weeks was used as the anchor, and an *a priori* literature review identified that a difference of greater that five GRCS points was considered clinically important. The first approach was based on sensitivity/specificity and the ability of the performance measure to correctly classify patients

as improved or not improved. The second was based on the within-patients performance measure score change that corresponded to patients who were defined as having shown major improvement in the GRCS. The third was based on the between-patients score change and was calculated as the difference in change score of patients showing major improvement in GRCS and those showing unimportant change.

The three methods used in the study identified borderline statistically significant (p=0.06) MCIDs for the TUGT of 0.8s (approach 1), 1.4 s (approach 2) and 1.2s (approach 3). In the absence of similar data for community dwelling frail older people, it is reasonable to surmise that the results derived from this study of older people receiving a nine-week physiotherapy intervention for hip osteoarthritis have implications for frail older people, including those recruited to the HOPE trial. If confirmed in a future definitive trial, an adjusted between group difference of 16.7s is therefore likely to be of clinical importance in relation to future change in health status. Furthermore, the more conservative estimate of an adjusted between-group difference of 5.3s derived from the sensitivity analysis is also likely to be clinically important.

Although not an *a priori* powered RCT, the sample size achieved in the HOPE trial is comparable to sample sizes achieved in two of the four high quality RCTs of home-based exercise interventions for frail older people identified in the systematic review (229, 230). To increase overall power,

it is possible to pool data from the HOPE trial with data from earlier trials of high methodological quality identified in the earlier systematic review for the outcomes of mobility and disability.

6.4.2 Pooling data from the HOPE trial with previous RCT data

6.4.2.1 Mobility

It is possible to pool data from the HOPE trial with TUGT data from one trial of high methodological quality identified in the earlier systematic review (229). Data in this trial were reported in the form of median (range). For the purposes of meta analysis, the mean was estimated to be equivalent to the median and standard deviation was estimated as range/4 (290). Mean differences were pooled using random effect inverse variance methods. Pooling of overall data demonstrated a non-significant trend towards a clinically unimportant difference (mean difference 1.2s, 95% CI -3.0, 5.5). The earlier trial was over a duration of six months, which may suggest that an early between group difference in TUGT at three months, as observed in the HOPE trial, may not be maintained over time. Although data were pooled a total sample size of 107 was obtained. Limitations of sample size are clearly still evident and the relationship between maintenance in TUGT and time requires further investigation.

6.4.2.2 Disability

It is also possible to pool data from the HOPE trial with disability data from one earlier trial of high methodological quality identified in the earlier systematic review (230). As outcome measurement tools were different, standardised mean differences (SMDs) were pooled using inverse variance random effects methods. The SMD is the difference in mean effects divided by the pooled standard deviation and therefore depends on the effect size and the individual standard deviations (291). A reasonable rule of thumb is that a pooled SMD value of 0.2 represents a small effect size, a value of 0.5 represents a moderate effect size and a value of 0.8 a large effect. A pooled SMD of 0.13 was obtained (95% CI -0.25, 0.51), indicating a probable small effect size.

Both trials were over a short duration. Interestingly, although a statistically significant between-group difference in disability score at seven months was reported in one previous RCT of high methodological quality, there was no statistically significant between-group difference at three months in the trial (227). It is reasonable to anticipate that, unless a sudden deterioration is encountered, a clinically meaningful between-group difference in TUGT may eventually translate into a clinically important difference in ADL score. In light of these data and the potential concerns regarding sensitivity to change of ADL instruments outlined above, appropriate length of follow-up should therefore be incorporated into a future definitive RCT to test the relationship between improvement in

mobility score and ADL. The relationship between maintenance of mobility and future disability will be considered in greater detail below.

6.4.3 The relationship between early maintenance of mobility and future disability

Loss of the ability to complete ADL is accompanied by an increased need for help from family members, friends or carers and predicts increased risk of hospitalisation, admission to long-term care and death (292, 293). A large prospective cohort study to observe the development and progression of ADL disability in 5151 participants reported a distinct hierarchy of dependency onset (294). This study used the order of incident disability recorded over a six year period in a US national probability sample of older people (mean age 78 years).

Total six year incidence rates for walking, bathing, transferring, dressing, toileting and feeding disabilities were 34%, 25%, 19%, 13%, 9% and 6% respectively, indicating that initial difficulties with walking (mobility) are likely to be followed, in order, by difficulties in bathing, transferring, dressing, toileting and feeding. The ordered median ages of disability onset were 84, 87, 90, 92, 93 and 100 respectively. Older women developed disability at earlier ages and experienced higher incidence rates of disability.

The authors of the study reported that the results differ from the Katz ordering of disability, which reports an initial onset of dependency in bathing followed by dependency in dressing, toileting, transferring, continence and feeding (295). However, the Katz hierarchy was developed in a cross-sectional study of 1001 younger and older people with a wide range of underlying diseases, including hip fracture, stroke, paraplegia, quadriplegia, cerebral palsy and motor neuron disease. As a hierarchical order must, by definition, be inferred from cross-sectional data a hierarchical order derived from longitudinal data is potentially more reliable (294). Of note, disability in transferring was recorded before disability in dressing and toileting in the longitudinal study when compared with the cross-sectional Katz study. As transferring requires strength in both upper and lower limbs, the ability to transfer is potentially more vulnerable to deterioration over time when compared to dressing, which requires only upper limb strength and dexterity. The results may indicate that lower extremity disability is likely to precede upper extremity disability in older age (294).

If the hierarchy of disability progression does indeed begin with difficulties with mobility and progress in an ordered manner over time it is therefore plausible that early maintenance of mobility, as recorded in the HOPE trial, may be associated with future maintenance of other ADL disabilities. Results from earlier trials would potentially support this possibility (227). This hypothesis requires evaluation in a future definitive RCT.

6.4.4 Risk of falls in the HOPE trial and previous research literature

There was no difference in risk of falls (risk ratio 0.93, 95% CI 0.29 - 2.93). In a meta-analysis of data from three trials including 566 participants a 2009 Cochrane review of home-based interventions for preventing falls in older people living in the community reported a pooled risk ratio of 0.77 (95% CI 0.61 - 0.97) (216).

6.5 Consideration of whether home-based exercise interventions are likely to improve outcomes for those who are most frail

A critical question is whether home-based exercise interventions are likely to improve outcomes for those who are most frail. The subgroup analysis identified that the overall between-group difference in TUGT was sustained in those who were considered to be most frail, as defined by the EFS. However, an earlier RCT of high methodological quality identified in the systematic review reported no improvement in disability score at three, seven or twelve months for those who were severely frail, defined using an operationalised measure of frailty (227).

Immunohistochemical and structural evidence of skeletal muscle remodelling in frail older people through exercise has previously been demonstrated (211). Critically, uncertainty remains regarding whether this biological improvement can eventually translate into clinically meaningful outcomes. Alternatively, as frail older people are at such high risk of sudden deterioration, it is possible that initial muscle remodelling and potential improvement in early mobility may not necessarily translate into an improvement in disability score when measured over a longer period of time. This critical question requires further investigation in a definitive RCT that incorporates both measurement of frailty in participants using a validated measure at baseline and an appropriate length of participant follow-up.

6.6 Implications for future research

The objectives of the HOPE trial were to

1) explore methods to identify frail older people in community settings;

2) assess the acceptability of the HOPE programme to frail older people;

3) test for a preliminary estimate of effectiveness;

4) test the feasibility of recording data to identify the therapy resources required to deliver the HOPE programme;

5) gather data to inform the design of a definitive clinical trial

The implications for future research will be considered in light of the HOPE trial objectives

6.6.1 Methods to identify frail older people in community settings

There is currently no proven reliable method to identify frailty as part of routine healthcare, which has made identification and recruitment of frail older people to the HOPE trial particularly challenging. Future research to test methods of identifying frailty to health and social care providers as part of routine care would greatly facilitate frailty research and potentially improve service provision for this vulnerable group.

At an early stage of trial recruitment, changes were made to the case manager service delivery model in south Bradford. Case managers, who had previously been based in the community, were moved at short notice into care homes, meaning that they were unable to identify additional participants for trial recruitment. This highlighted the importance of considering alternative methods of participant recruitment, particularly when a relatively new model of care that is subject to change is used to identify potential participants for clinical trials.

6.6.2 The acceptability of the HOPE programme to frail older people

Approximately 1/4 of those approached were successfully recruited into the HOPE trial. Although recruitment rates were lower than the majority of previous RCTs identified in the earlier systematic review this may reflect different inclusion/exclusion criteria and methods of approach. Although beyond the scope of this study, future research to better understand the reasons why many frail older people decline to take part in trials of home-based exercise interventions is of particular importance. Training of those who undertake trial recruitment in behaviour change methods may be one strategy to help facilitate recruitment of frail older people to future RCTs.

Although partial intervention compliance was relatively high, total intervention compliance was lower, suggesting that a proportion of participants found the intervention intensity of three times a day on five days of the week too much. It is therefore likely that a period of further intervention modelling work will be required before the HOPE programme can be tested in a future definitive RCT, to gain additional insight into the optimal intensity of a home-based exercise intervention for frail older people.

6.6.3 A preliminary estimate of effectiveness

The pilot HOPE trial has provided the necessary information required for a preliminary estimate of intervention effectiveness. By design, the pilot HOPE trial was not based on an *a priori* sample size calculation. This means that any result that achieves statistical significance would be an unexpected chance result and hypothesis testing by calculation of p values is therefore not indicated. Instead, a carefully considered narrative interpretation of estimates of effect size with confidence intervals is warranted.

There was a non-significant trend towards a clinically meaningful improved outcome in the intervention group (mean adjusted between group difference in TUGT 16.7s, 95% CI -33.3, 66.6s) that was robust to sensitivity analysis. There were no differences in any of the secondary outcomes and no differences in adverse outcomes, which may reflect concerns regarding the sensitivity to change of the secondary outcome measures over a 14 week period. The preliminary estimates of effectiveness and variance provides the necessary information that is required for the sample size calculation for a future definitive trial.

6.6.4 The feasibility of recording data to identify the therapy resources required for delivery of the HOPE programme

Although the physiotherapists delivering the HOPE programme were requested to include the time taken to deliver the HOPE programme at each home visit, the time taken for travel to and from the home of the participant and the time taken for each telephone call this important data was not initially recorded. The simple addition of dedicated boxes for the recording of this information on the therapy record, along with written instructions to therapists, has helped facilitate collection of this information for the more recent trial participants.

6.6.5 Data to inform the design of a definitive clinical trial

The pilot HOPE trial has provided the necessary data to help design a future definitive randomised controlled trial of a home-based exercise intervention for frail older people. Assuming a two-sided α level of 0.05, a future trial with 351 participants would have 80% power to detect a difference of 18.0s in the TUGT. On the basis of the more conservative estimates from the sensitivity analysis, assuming a two-sided α level of 0.05, a future trial with 463 participants would have 80% power to detect a difference of 5.3s in the TUGT. Assuming withdrawal rates of 13%, the sample sizes would require inflation to 397 and 523 respectively.

As discussed previously, future RCTs of complex interventions for frail older people should consider the importance of including a sham intervention where possible, to help maintain assessor blinding. Future RCTs that measure change scores should consider whether outcome measures are suitably sensitive to change, and consider incorporation of long-term follow-up to investigate important outcome measures including disability, quality of life, hospitalisation and admission to long-term care.

6.7 Implications for clinicians and commissioners

The HOPE trial has identified that home-based exercise interventions are acceptable to frail older people and feasible to deliver. The trial provides evidence of the potential benefit of exercise in frailty, but this provisional evidence requires confirmation in a future definitive trial.

There is robust evidence for the effectiveness of falls prevention interventions for older people living in the community, including home-based falls prevention interventions for older people (216, 223). However, on the basis of the evidence from the HOPE trial, commissioning of home-based exercise interventions for frail older people cannot be recommended until they have been demonstrated to be both clinically and cost-effective.

6.8 Conclusion

The HOPE trial has identified that a home-based exercise intervention for frail older people is feasible, acceptable and safe. The trial has provided preliminary evidence that the deterioration in mobility experienced by frail older people can potentially be diminished through exercise. This preliminary evidence requires confirmation in a future definitive, adequately powered RCT that incorporates long-term follow-up of important outcomes including disability, quality of life and admission to hospital and long-term care. The HOPE trial has provided valuable process, resource, management and scientific data to guide the development of a future definitive RCT and has provided important information to help inform future research involving frail older people.

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8 Appendices

Appendix 1. Full systematic review search strategy.

Trials were identified by searching Medline 1950-Jan week 3 2010, AMED 1985-Jan 2010, CINAHL 1981 to Jan2010, Cochrane Library Issue 1 2010,EMBASE 1947-Feb 2010, PSYCINFO 1806-Jan week 4 2010 and PedRO to Jan2010. We did not confine our search to English language publications. The Cochrane Highly Sensitive Search Strategy for identifying randomised trials in Medline (Higgins, 2008 http://www.cochrane-handbook.org/) was combined with the following search terms to identify RCTs in Medline. The Medline search strategy was adapted for use in the other databases searched.

MEDLINE strategy:

1. early ambulation/ or exercise therapy/ or muscle stretching exercises/ or resistance training/ or occupational therapy/
2. physical therapy modalities/ or musculoskeletal manipulations/
3. "Physical Therapy (Specialty)"/
4. Exercise Movement Techniques/
5. Exercise/
6. "Physical Education and Training"/
7. Physical Fitness/
8. "Recovery of Function"/
9. Physical Stimulation/

10. Health Promotion/

11. rehabilitation/

12. walking/

13. locomotion/

14. (rehabilitat$ or exercise$ or physiotherap$ or keep fit).tw.

15. (physical adj3 (therap$ or education or train$ or stimulat$ or fitness or activit$ or function)).tw.

16. ((exercise or movement or occupational) adj3 (therap$ or train$ or treatment or program$)).tw.

17. ((strength$ or aerobic or resistance) adj3 activit$).tw.

18. (improve$ adj3 (function or mobil$ or recover$)).tw.

19. ((fitness or health) adj3 promotion).tw.

20. ((endurance or balance or strength or flexibility or resistance) adj3 training).tw.

21. walk$.tw.

22. or/1-21

23. exp Aged/

24. (elder$ or older or oldest or old age or senior$ or geriatr$ or gerontol$ or aging or ageing or late life).tw.

25. Geriatric assessment/

26. or/23-25

27. (community adj3 (live or living or dwell$ or based)).tw.

28. (independen$ adj3 (live or living or dwell$ or based)).tw.

29. (sheltered adj (hous$ or accomm$ or home$ or living)).tw.

30. ((home or communit$) adj5 (caring or care$)).tw.

31. (community adj (nurs$ or matron$)).tw.

32. (housebound or house-bound or home-bound or homebound or home-based or homebased).tw.

33. Homebound Persons/

34. "Home Care Services"/

35. independent living/

36. activities of daily living/

37. or/27-36

38. randomized controlled trial.pt.

39. controlled clinical trial.pt.

40. randomized.ab.

41. placebo.ab.

42. drug therapy.fs.

43. randomly.ab.

44. trial.ab.

45. groups.ab.

46. 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45

47. humans.sh.

48. 46 and 47

49. 26 and 37

50. 22 and 49

51. 48 and 50

Appendix 2. Key research questions that informed the semi-structured interview schedules.

Focus Groups 1 & 2

What factors contribute to daily functional limitations in frail older people living at home?

How is the concept of exercise in old age understood by frail older people?

What are frail older people's perceived barriers to involvement in a targeted exercise programme?

What should the intensity be of an exercise programme designed to improve the functional status of frail older people living at home?

What would motivate frail older people living at home to complete a targeted exercise programme lasting 12 weeks?

Focus Group 3

1) What limitations in functional ability do you see in your patient group of frail older people?

2) What types of exercises are likely to be effective at improving functional abilities of frail older people living at home?

3) What do you think would motivate/aid frail older people to adhere to a home-based exercise training programme?

4) What do you think are potential barriers to exercising in the home for frail older people?

5) What should be the design (intensity/frequency/duration) of an exercise programme aimed at improving the functional status of frail older people living at home?

Appendix 3. Sample questionnaire used in Delphi round two.

Strongly disagree Neutral Strongly agree

1 2 3 4 5 6 7 8 9

1) There is a large amount of variation in the functional abilities of frail older people living at home. ☐

2) Thought needs to be given to this variation when designing an exercise programme to improve the functional abilities of frail older people living at home i.e. a 'one size fits all approach' is inappropriate. ☐

3) Older people are commonly limited by
   a) lower limb weakness ☐
   b) poor postural flexibility/stability. ☐

4) These limitations are often expressed functionally by difficulty in standing from a chair and difficulty climbing stairs. ☐

5) Older people will require face-to-face contact on more than one occasion to help learn a structured exercise programme and improve compliance. ☐

6) The exercise programme needs to be simple. ☐

7) It is important to
   a) include goal setting in the exercise programme ☐
   b) monitor success/benefit throughout the exercise programme ☐
   c) allow participants to advance during the exercise programme. ☐

8) Key perceived barriers to participation are likely to be
   a) respiratory problems ☐
   b) joint stiffness/joint pain ☐
   c) low mood. ☐

9) Flares of chronic medical diseases may impact on participation in the exercise programme. ☐

10) Potential measures to improve involvement/compliance include

a) Allowing adaptation to the exercise programme, i.e. if a participant is feeling unwell then they should complete the warm-up exercises only
b) Attempting to incorporate the programme into normal daily routine
c) Making the programme meaningful to the individual
d) Engaging with & involving family/carers
e) Using different levels of exercise (e.g. chair based/standing) depending on the ability of the individual

Appendix 4. Example pages used in information provision needs assessment exercise.

Patient Handout

Improve Your Balance in 10 Minutes a Day

Four Square

An important part of the balance system you use every day is your ability to know where certain body parts are in space. Your "internal sense of spatial orientation" is helped by this exercise.

1. Get on all fours with knees and hands 12 inches apart.
2. Keep your back flat and your head "straight."
3. Lift each arm forward by itself and hold for 5 to 10 seconds.
4. Repeat with each leg, straightening it behind you but keeping it close to the ground.
5. Lift the opposite arm and leg (right arm, left leg) at the same time and hold for 10 seconds. Then repeat on the opposite side.

Posture Perfect

Posture and strength are important components of your body's system of maintaining balance. These exercises encourage good posture while enhancing lower extremity strength as well.

1. Stand with your arms resting comfortably with a countertop or sturdy table in front of you and a wall behind you.
2. Stand with your feet comfortably apart. Look straight ahead, keep your back straight and your knees slightly bent.
3. Slowly rise up on your toes.
4. Lower yourself down slowly and repeat 5 times.
5. Keep your posture the same, but this time raise the front part of your foot, lower it slowly, and repeat 5 times.
6. Finally, keep standing as you have been. Lift one leg several inches off the floor and hold for 5 seconds, lower it slowly, and repeat 5 times. Repeat on the opposite foot.

For more information on The AGS Foundation for Health in Aging call 1-800-563-4916 or visit www.healthinaging.org.

This handout is excerpted from the Falls in Older Adults Primary Care Practice Toolkit developed by the Practicing Physician Education Project which was supported by a grant from the John A. Hartford Foundation through the American Geriatrics Society.

Example 1. Patient handout: improve your balance in 10 minutes a day. The American Geriatrics Foundation for Health in Aging.

PATIENT HANDOUT

Notes

The purpose of this patient education handout is to further explain or remind you about a medical condition. This handout is a general guide only. If you have specific questions, be sure to discuss them with your health care provider.

advance FOR DIRECTORS IN Rehabilitation

WEB EXCULSIVE

Patient Handout: Balance and Fall Prevention

Falls are a leading cause of injury and death in adults over the age of 65. One in four persons over the age of 65 will fall in their home. Falls often result in fractures of the hip and hand.

Older adults are especially at risk because of balance impairments. However, several other factors may increase the risk of falling, including poor strength, medications and dizziness. Environmental factors, such as slippery surfaces or obstacles in the home, can also be a problem.

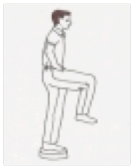
EXERCISES TO IMPROVE BALANCE

*Perform exercises on a firm surface. For standing exercises, use a chair or other support to help maintain balance. To increase difficulty, you can progress to a stability trainer device.

STANDING EXERCISES

One-Leg Balance
Balance on one leg.
Repeat on the other leg.
Begin on a firm surface.

Calf Raise
Balance on one leg.
Go up onto your toes.
Repeat on the other leg.

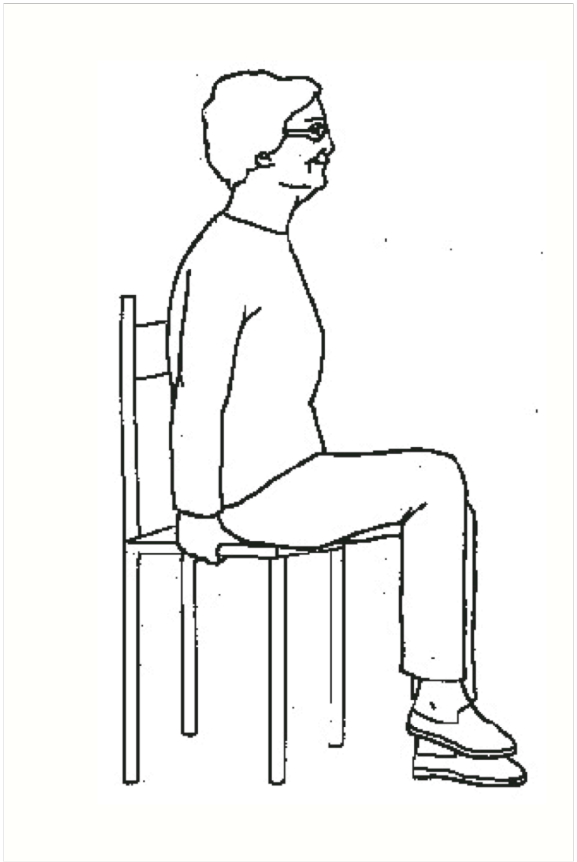


Hip Raise
Balance on one leg.
Lift your hip upward.
Repeat on the other leg.

Hip Extension
Balance on one leg.
Extend your hip behind your body.
Repeat on the other leg.

Knee Bend
Balance on one leg.
Bend your knee.
Repeat on the other leg.

Example 2. Patient handout: balance and fall prevention. Advance for Directors in Rehabilitation.



1 Chair march

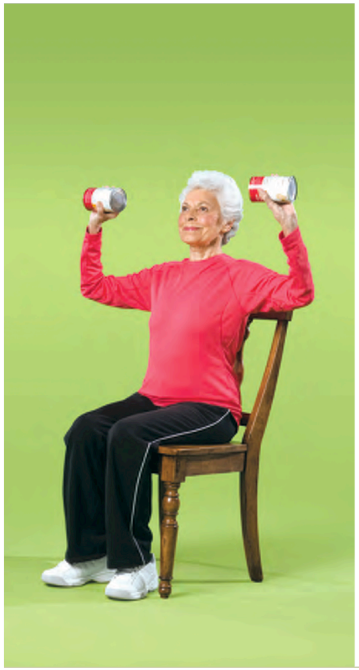
- Sit tall
- Hold the sides of the chair
- Alternately lift your feet and place them down *with control*
- Build to a rhythm that is comfortable for you
- Continue for 30 seconds

3

Example 3. Preventing falls: strength and balance exercises for healthy ageing. AgeUK.

This exercise will strengthen your shoulders and arms. It should make swimming and other activities such as lifting and carrying grandchildren easier.

Overhead Arm Raise



1. You can do this exercise while standing or sitting in a sturdy, armless chair.
2. Keep your feet flat on the floor, shoulder-width apart.
3. Hold weights at your sides at shoulder height with palms facing forward. Breathe in slowly.
4. Slowly breathe out as you raise both arms up over your head keeping your elbows slightly bent.
5. Hold the position for 1 second.
6. Breathe in as you slowly lower your arms.
7. Repeat 10-15 times.
8. Rest; then repeat 10-15 more times.

TIP

As you progress, use a heavier weight and alternate arms until you can lift the weight comfortably with both arms.

Example 4. Exercise and physical activity. US Department of Health and Human Services. National Institute of Health. National Institute on Aging.

Appendix 5. HOPE programme physiotherapist timeline.